Phytomedicine Plus 4 (2024) 100549

Contents lists available at ScienceDirect

Phytomedicine Plus

journal homepage: www.sciencedirect.com/journal/phytomedicine-plus

Terpenoids in essential oils: Chemistry, classification, and potential impact on human health and industry

Tohfa Siddiqui [a,*], Mohammad Umar Khan [b], Vikram Sharma [a], Komal Gupta [a]

[a] Galgotias college of pharmacy, Knowledge park-II, greater Noida, 201306, India
[b] Department of Food Technology, School of Interdisciplinary Science and Technology, Jamia Hamdard, New Delhi, 110062, India

ARTICLE INFO

Keywords:
Terpenoids
Essential oils
Bioactive compounds
Human health
Pharmacological effects

ABSTRACT

Background: Terpenoids, present in essential oils (EOs), have gained significant attention due to their diverse pharmacological properties and their alignment with the growing global interest in natural and sustainable products. EOs, derived from various plants, have shown promise in antimicrobial, anti-inflammatory, antioxidant, and other valuable applications.
Aim of the Study: This comprehensive review aims to elucidate the chemistry and pharmacological roles of terpenoids and EOs, covering their classification, extraction techniques, and potential pharmaceutical applications. We delve into their functions in the human immune system, their impact on health, and their contributions to environmental sustainability.
Materials and Methods: The review synthesizes existing literature, categorizing terpenoids into distinct classes, including monoterpenoids, sesquiterpenoids, diterpenoids, sesterterpenoids, and triterpenoids. We explore various extraction and purification methods, such as steam distillation, solvent extraction, and chromatography. Additionally, we discuss the pharmacological properties of terpenoids, including their antioxidant, antimicrobial, and anticancer activities.
Results: Terpenoids and EOs exhibit potent antimicrobial and antioxidant activities, making them pivotal in plant disease resistance. They also offer potential therapeutic applications in phytomedicine, aromatherapy, and beyond, with the capacity to enhance the human immune system and combat viruses, inflammation, and cancer.
Conclusion: Terpenoids and EOs have demonstrated multifaceted pharmacological benefits, contributing to human well-being and environmental sustainability. This review highlights their potential in medical treatments and everyday life, emphasizing the need to understand their pharmacokinetics and efficacy for harnessing their full potential in pharmaceutical applications and beyond.

1. Introduction

Terpenoids in essential oils are key bioactive compounds driving the global embrace of natural products. They offer aromatherapy, anti-inflammatory, antimicrobial effects, and more, encouraging holistic, sustainable living. Their popularity reflects a collective appreciation for nature's wonders and a desire for healthier, eco-conscious lifestyles (Fotsing Yannick Stephane and Kezetas Jean Jules, 2020). Essential oils are potent and concentrated hydrophobic liquids obtained from various plants, each classified based on distinct chemical and physical characteristics. These EOs have undergone extensive research to explore their pharmacological effects, which span a wide range of applications. They have demonstrated properties such as antimicrobial, anti-helminthic, antiviral, antiulcer, antioxidant, anti-inflammatory, insecticide, and larvacidal actions. Their versatility and diverse benefits make them valuable compounds with potential applications in various fields, from medicine to pest control and more (Dhifi et al., 2016). Terpenes, including pinene, myrcene, limonene, terpinene, and p-cymene, have simple hydrocarbon structures, while terpenoids are modified versions with oxygen-containing hydrocarbons and oxidized methyl groups

Abbreviations: BAX, Bcl-2-associated X; Bcl-2, B-cell lymphoma 2; COVID-19, Coronavirus 2 (SARS-CoV-2); COX, Cyclooxygenase; CsA, Cyclosporine; CL, *Curcuma longa*; DNFB, Dinitroflurobenzen; IL, Interleukin; I.p, Intraperitoneally; LPO, Lipid peroxidation; MAPK, Mitogen- activated protein kinase; MDA, Malondialdehyde; MVM, Mevalonate pathways; NF-Kβ, Nuclear factor kappa β; $P_{I3}K$, Phosphoinositide 3-kinase; ROS, Reactive oxygen species; SOD, Superoxide dismutase; STZ, streptozotocin; TNF-α, Tumor necrosis factor; TCDD2-3-7-8, Tetrachlorodibenzo-p-doxin; THQ, Thymohydroquinone.

* Corresponding author.
E-mail address: tohfa@galgoticollege.edu (T. Siddiqui).

https://doi.org/10.1016/j.phyplu.2024.100549

Available online 24 March 2024

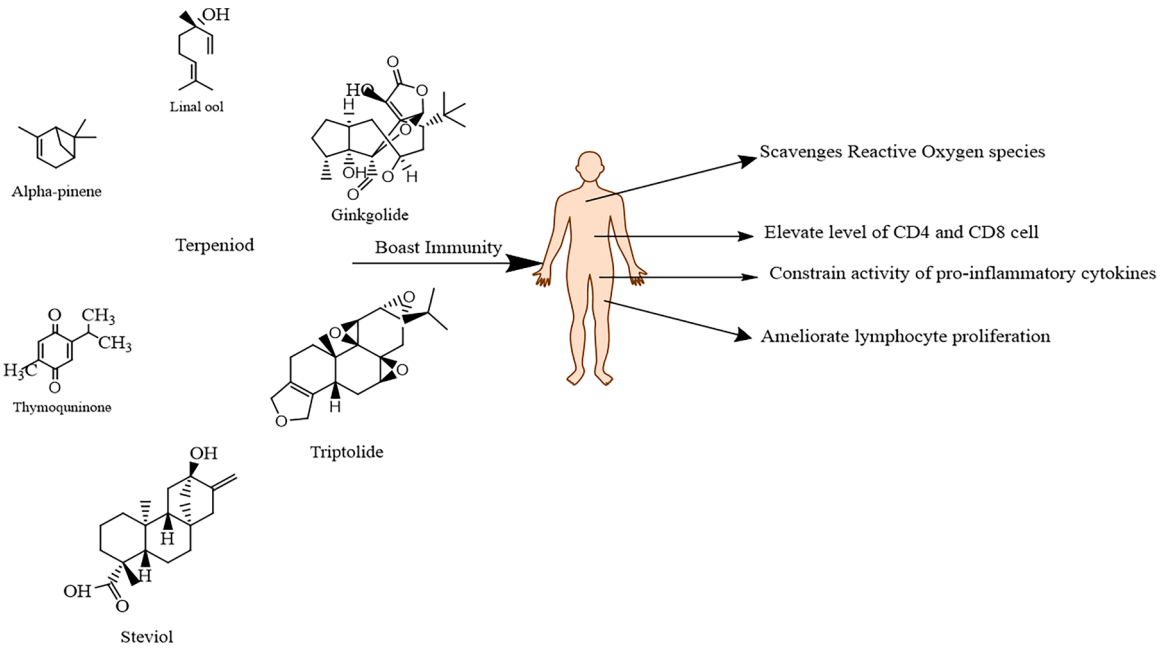

Fig. 1. Immunomodulator properties of different terpenoids in medicinal plant and herbs.

moved or removed at different positions. Terpenes exhibit antimicrobial activities against antibiotic-susceptible and antibiotic-resistant bacteria, disrupting cell function and inhibiting protein and DNA synthesis. Specific terpenes like carvacrol, carvone, eugenol, geraniol, and thymol have demonstrated antibacterial action against Staphylococcus aureus (Masyita et al., 2022). Terpenoids, as secondary metabolites in aromatic and medicinal plants, play a crucial role in disease resistance. Monoterpenoids, for example, act as antibacterial agents, disrupting microbial growth and interfering with their physiological activities. Compounds like azadirachtin, carvone, menthol, ascaridol, methyl eugenol, toosendanin, and volkensin display antimicrobial, antifungal, and insect repellent properties (Masyita et al., 2022).

In recent years, there has been an increasing focus on plant essential oils (EOs) in both phytomedicine and aromatherapy, leading to widespread use and garnering significant interest from scientists in basic research. Their antimicrobial, antioxidant, and anticancer activities have been particularly intriguing for researchers. Essential oils are complex mixtures of chemicals comprising numerous types of molecules, with terpenes and phenylpropanoids (benzene derivatives) being the main components responsible for their biological effects. Although terpenes and essential oils share some similarities, such as being derived from plants and having aromatic properties, they are not necessarily the same and serve different purposes. The misconception that they are identical has arisen due to these resemblances, but it's crucial to recognize their distinct characteristics and functions (Butnariu and Sarac, 2018). In addition, essential oils derived from plant also act as a Immunity booster. Immunity is a highly coordinated set of processes involving molecules, cells, and tissues, aimed at maintaining the stability of an organism. Its primary function is to identify and respond to the presence of pathogens, distinguishing between what is intrinsic to the organism and what is foreign. The immune system has evolved to confront and eliminate invaders or abnormal components within the body, such as tumors, while preserving the integrity of healthy cells. In vertebrates, the immune system is a complex and sophisticated defense mechanism that incorporates both sensory and effector mechanisms mediated by receptors. It is commonly categorized into two major types: innate immunity and adaptive immunity. These two forms of immunity work in tandem to provide a comprehensive defense against pathogens, ensuring the survival and well-being of the organism.

Natural products have been broadly exploited as an important source for medicine. A large number of medicines and essential oils are derived from plant-based extractions and fractionation and have great importance for humans. Nowadays, medical practitioners are more inclined towards natural medicines and essential oils for a trustworthy treatment with cost effectiveness and lower incidence of side effect. Micronutrients which are present in essential oils, including minerals like iron (Fe), zinc (Zn), and calcium (Ca), have a diverse range of therapeutic potential. These minerals play a vital role in enhancing the immune system, protecting against viral infections, and maintaining the body's overall balance. Moreover, numerous researchers have extensively studied these micronutrients to uncover their pharmacological properties, such as their ability to combat viruses, reduce inflammation, fight cancer, act as antioxidants, and regulate blood sugar levels in diabetes. The main sources of phytochemicals include vegetables, fruits, seeds, spices, whole grains, herbs, legumes, shrubs, trees. They are maintained and positioned in various plant components at varying amounts, such as seeds, fruits, stems, bark and leaves (Lourenço et al., 2019). When we look into the classification, we see there is not a consistent classification system so far and this is because vast number of phytochemicals discovered or add up every year. A simplistic classification method divides phytochemicals into three separate categories. They are terpenes, phenolics, Nitrogen containing, Sulfur compound (Mendoza and Silva, 2018) **(**Fig. 1**).** This review aims to present a comprehensive understanding of the potential role of terpenes and terpenoids, which are the main bioactive compounds found in essential oils (EOs), in relation to human health and their industrial application as natural food preservatives. By exploring this topic, we can uncover exciting possibilities and research directions that may lead to widespread pharmaceutical applications of the constituents found in Eos and terpeniod, as well as various extraction technique of essential oils thus benefiting our daily **lives.** In addition, it is essential to include ADME analysis (Absorption, Distribution, Metabolism, and Excretion) of terpenoids sourced from plant materials in the context of essential oils. This analysis helps to assess the pharmacokinetic properties and potential efficacy of terpeniods as main bioactive component of essential oil.

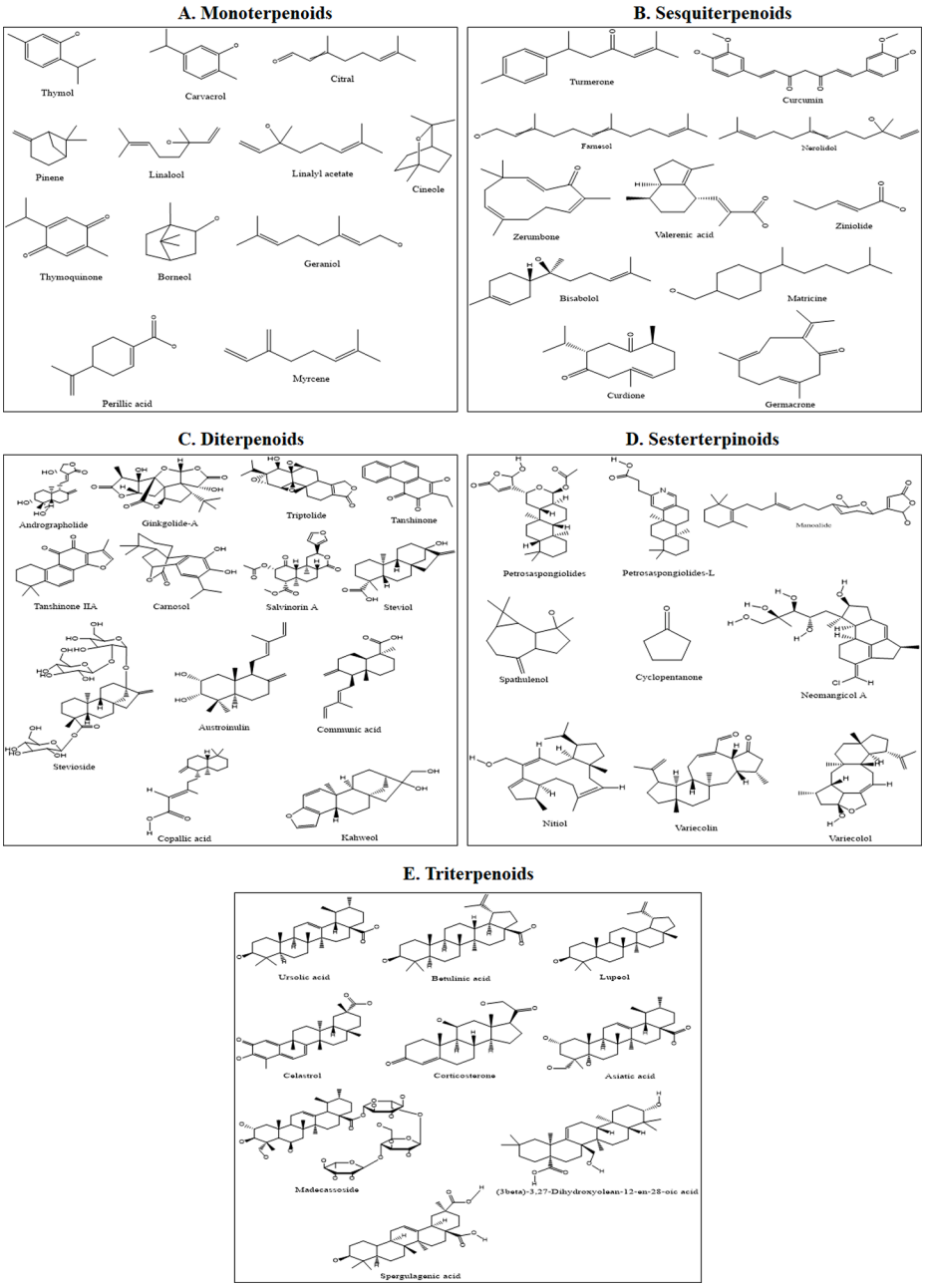

Fig. 2. Structure of monoterpenoid, Sesterterpenoids, Diterpenoids, Sesterpenoids Triterpenoids.

2. Review finding

2.1. Chemistry of terpenoids and essential oils

Terpenoids are a diverse class of naturally occurring organic compounds that are derived from the five-carbon isoprene unit (C_5H_8). The isoprene unit consists of two methyl groups (CH_3) attached to two double bonds, which play a crucial role in the reactivity and stability of terpenoids. They are known for their strong odors and are responsible for the characteristic scents of many plants, essential oils, and resins. Terpenoids play essential roles in various biological functions and have a wide range of pharmacological activities (Masyita et al., 2022). Essential oils are complex mixtures of volatile organic compounds, which means they have low boiling points and readily evaporate at room temperature. These compounds are responsible for the characteristic aroma and flavor of the essential oils. Terpenoids are the major constituents of essential oils. Monoterpenoids and sesquiterpenoids are the most common terpenoid classes found in essential oils. These compounds are derived from isoprene units (C_5H_8) and often have cyclic or acyclic structures. In addition to terpenoids, essential oils may also contain oxygenated compounds, such as alcohols, aldehydes, ketones, esters, and phenols. These compounds are formed through various biosynthetic pathways in plants and contribute to the unique aroma and therapeutic properties of essential oils. The chemical composition of essential oils can vary significantly depending on factors such as the plant species, the part of the plant from which the oil is extracted, the geographical location, climate, and harvesting time. These variations can lead to subtle differences in the aroma and properties of the oils(Bunse et al., 2022).

2.2. Classification of terpenoids

2.2.1. Monoterpenoids ($C_{10}H_{16}$) chemical structures and functions

Monoterpenoids are a type of compounds that are made up of two isoprene units giving them the formula C10H16. These monoterpenoids

Table 1
Molecular mechanism of different terpenoids.

S. No	Class	Name of compound	Molecular Mechanism	Immunomodulatory Activities	Other Biological Activities	Reference
1	Monoterpenoid	Thymol	Enhancing immune response by increasing hypersensitivity & decreasing hetrophils/lymphocytes ratio	Immunostimulant, Anti-inflammatory, Antimicrobial, Antioxidant, Antiviral	Analgesic, Anti-fungal, Gastroprotective, Anticancer, Chemo preventive	(Nagoor Meeran et al., 2017)
		Carvacrol	Inhibit peripheral mediators & decreases TNF-α production	Anti-inflammatory, Antimicrobial, Antioxidant, Antiviral	Neuroprotective, Anticancer, Anxiolytic, Antinociceptive	(Guimarães et al., 2012)
		Citral	Inhibit IL-1β production when incubated earlier than LPS	Anti-inflammatory, Antimicrobial, Antioxidant	Insecticidal, Anticancer, Anxiolytic	(Ka et al., 2015)
		α-Pinene	Activate lymphocyte through CD69 & phagocytic activity, also stimulate NO production & have potential immunomodulating effects on NKCA	Immunomodulator, Anti-inflammatory, Antioxidant	Bronchodilatory, Anticancer, Neuroprotective	(De Cássia Da Silveira E Sá et al., 2013)
		D-Limonene	Preclinical study: D-limonene inhibits lymphocyte proliferation at high dose. In vitro study: D-limonene inhibit the production by $CD3^+$ $CD4^+$ T cells of IFN-γ,IL-2,TNF-α,IL-4 & IL-13	Immunomodulatory, Anti-inflammatory, Anticancer, Antioxidant	Gastroprotective, Chemopreventive, Anxiolytic, Antinociceptive	(Nagoor Meeran et al., 2021)
		Linalool	Shows potential immunomodulating effects on NKC (Natural killing cell) as well as lymphocyte activation through CD69 expression	Immunomodulator, Anti-inflammatory, Antioxidant	Anxiolytic, Sedative, Anticancer	(Borrego et al., 1999)
		Linalyl acetate	Stimulate natural killing cell activity (NKCA0	Immunomodulator, Anti-inflammatory, Antimicrobial, Antiviral	Anxiolytic, Sedative, Anticancer	(Standen et al., 2006)
		Cineole or 1,8-Cineole	Decreases $CD8^+$ cells levels,increases $CD3^+$,$CD4^+$,$CD161^+$,$CD4^+$+$CD25^+$ cells levels. Also effectively suppressing monocyte & lymphocyte productionof two cytokines TNF-α & IL-1β	Immunomodulator, Anti-inflammatory, Antioxidant	Bronchodilatory, Antifungal, Analgesic	(Pesenacker et al., 2013)
		Thymoquinone & Thymohydroquinone	Stimulate immune system, show respiratory stimulatory effects by increasing the number of T helper type 2 (Th2) cytokine levels (IL-4, IL5 & IL-13), eosinophils, mast cells & production of IgE	Immunomodulatory, Anticancer, Anti-inflammatory, Antioxidant	Respiratory stimulant, Antihistaminic, Antiviral	(Koshak et al., 2018)
		Borneol, 1-borneol, 1-bornyl acetate	Decreases the levels of NO, increases iNOs enzymatic activity, increased levels of $CD4^+$ & $CD8^+$ T lymphocytes, IFN-γ was found in the study of LPS induced abortion mice	Immunomodulatory, Anti-inflammatory, Antioxidant	Neuroprotective, Cardioprotective, Antimicrobial	(Yang et al., 2014)
		Geraniol	lymphocyte proliferation shows a conc-dependent inhibition of lymphocyte proliferation, results shows gerniol has the modest in vitro in vivo immunosuppressive activity	Immunomodulatory, Anti-inflammatory, Antioxidant	Anticancer, Antimicrobial	(Flaminio and Antczak, 2005)
		Perillic acid	Increased total white blood cells (WBC) counts, total antibody (IgE) producing cells in spleen & bone marrow cellularity and enhance effects on immune system	Immunomodulatory, Anticancer, Antioxidant	Chemopreventive, Antiviral	(Raphael and Kuttan, 2003)
		β- Myrcene	Shows immunoregulatory activity by effectively inhibiting NO production of IFN-γ & IL-4	Immunomodulatory, Anti-inflammatory, Antioxidant	Anxiolytic, Antinociceptive	(Ubessi et al., 2019)
2	Sesquiterpenoids	Turmerone	Inhibits MMP-9,COX-2 & NF-κ B, Suppresses COX-2 & iNOS	Anti-inflammatory, Antioxidant, Anticancer, Neuroprotective	Antifungal, Hepatoprotective, Cardioprotective	(Park et al., 2012)
		Curcumolide	Decreases TNF-α, IL-6, IL-1β & reduces NO production	Anti-inflammatory, Antioxidant	Anticancer, Antimicrobial, Hepatoprotective	(Dong et al., 2015)
		Farnesol	Increases IL-10 in preclinical studies of asthmatic inflammation	Immunomodulatory, Anti-inflammatory, Antioxidant	Antimicrobial, Anticancer, Antioxidant, Wound healing	(Ku and Lin, 2015)
		Nerolidol	Decreases IL-13 & TNF-α	Anti-inflammatory, Antioxidant	Antifungal, Anticancer, Antimicrobial, Anxiolytic	(Choi et al., 2017)
		Zerumbone	Inhibits NF-κ B via inhibiting IκBα Degradation	Anti-inflammatory, Anticancer, Antioxidant	Antimicrobial, Antiviral, Hepatoprotective, Neuroprotective	(Weng et al., 2012)
		Valerenic acid	Inhibits NF-κ B signaling	Anti-inflammatory, Antioxidant, Neuroprotective	Anticancer, Cardiovascular protective, Antiplatelet, Anxiolytic	(Kara et al., 2021)
		Ziniolide	Inhibits 5-LOX & NF-κ B activity	Immunomodulator, Anti-inflammatory, Anticancer, Antioxidant	Nephroprotective, Anticancer, Anti-inflammatory	(Kara et al., 2021)

(*continued on next page*)

Table 1 (*continued*)

S. No	Class	Name of compound	Molecular Mechanism	Immunomodulatory Activities	Other Biological Activities	Reference
		α-Bisabolol	Decreases carrageenan-induced paw edema & leukocyte migration & TNF-α	Immunomodulator		(Kara et al., 2021)
		Matricine	Inhibits NF-κ B transcriptional activity	Immunomodulator		(Flemming et al., 2015)
		Curdione	Inhibits PGE_2 via COX-2 suppression	Immunomodulator		(Oh et al., 2007)
		Germacrone	Inhibits NO production, anti-inflammatory against carrageenan	Immunomodulator		(Liao et al., 2013)
3	Diterpenoids	Andrographolide	Increases lymphocyte number. Increase production of IL-2, IFN-γ by T cells & NK cells, inhibit tumor's growth, regulate production of antibodies & generation of antigen-specific splenocytes	Immunostimulant, Anti-inflammatory, Anticancer, Antioxidant	Antiviral, Hepatoprotective, Cardiovascular protective	(Carretta et al., 2009)
		Ginkgolides	Inhibit NF-κB activation & production of proinflammatory cytokine	Anti-inflammatory, Antioxidant, Neuroprotective	Anticancer, Cardiovascular protective, Antiplatelet, Anxiolytic	(Li et al., 2017)
		Triptolide	Modulate the T-cell response & inhibit IL production in vitro	Immunomodulator, Anti-inflammatory, Anticancer, Antioxidant	Nephroprotective, Anticancer, Anti-inflammatory	(Tamgue et al., 2021)
		Tanshinone Tanshinone IIA	Inhibit prostaglandin & leukotriene production,Inhibits NF-κ B,	Anti-inflammatory, Antioxidant, Cardiovascular protective, Hepatoprotective	Nephroprotective, Anticancer, Antimicrobial, Neuroprotective	(Ding et al., 2020)
		Carnosol	Decreased NO production, reduces iNOS expression	Anti-inflammatory, Antioxidant, Neuroprotective	Anticancer, Cardiovascular protective, Nephroprotective	(Schwager et al., 2016)
		Salvinorin A	Inhibits lekotriene synthesis	Anti-inflammatory, Antimicrobial, Antioxidant, Antiviral	Neuroprotective, Anticancer, Anxiolytic, Antinociceptive	Rossi et al 2016
		Steviol & stevioside	Decrease proinflammatory cytokine (TNF-α, IL-1β, IL-6) production	Anti-inflammatory	Anticancer, Cardiovascular protective, Nephroprotective	(Noosud et al., 2017)
		Austroinulin	Block NF-κ B activation, Inhibit iNOS expression & NO production	Anti-inflammatory	Anticancer, Nephroprotective	(Cho et al., 2013)
		Communic acid & copallic acid	Inhibit COX & COX-2 expression	Anti-inflammatory	Anticancer, Cardiovascular protective, Antiplatelet, Anxiolytic	(Ribeiro et al., 2019)
		Kahweol	Inhibit COX-2 expression & MCP-1 secrection	Anti-inflammatory, Immunomodulator activity	Anticancer, Nephroprotective	(Cárdenas et al., 2011)
		Gingival fibroblasts	Inhibited NF-κ B activation	Anti-inflammatory, Immunomodulator activity	Anticancer, Cardiovascular protective	(Zhou et al., 2021)
4	Sesterterpinoids	Petrosaspongiolides	Inhibit action against PLA_2 enzymes,	Anti-inflammatory, Immunomodulator activity	Anticancer, Cardiovascular protective, Nephroprotective	(Garcia-Pastor et al., 1999)
		Petrosasponiolides	inhibit tumor proliferation in vivo	Anti-inflammatory Immunomodulator activity,	Anticancer, Nephroprotective	(Olsson et al., 2004)
		Manoalide	Block the action of PLA_2	Immunomodulatory, Anti-inflammatory, Anticancer, Antioxidant	Anticancer, Cardiovascular protective, Nephroprotective	(Chang et al., 2019)
		Spathulenol	Reduces proliferation of lymphocytes, Stimulate peripheral blood lymphocytesa & induce apoptosis	Anti-inflammatory, Antioxidant, Neuroprotective	Anticancer, Nephroprotective	(Ziaei et al., 2011)
		Cyclolinteinone	Prohibit NO synthase & blocking nuclear factor kappaB activation in J7774 macrophages	Imm Antioxidant, Neuroprotective unomodulator	Anticancer, Cardiovascular protective, Nephroprotective	(de las Heras and Hortelano, 2009)
		Neomangicols	Shows cytotoxicty against HCT-116 human colon carcinoma in vitro	Antioxidant, Neuroprotective	Anticancer, Cardiovascular protective, Nephroprotective	(Gurunathan et al., 2018)
		Nitiol	Powerful enhancer of IL-2 gene expression in human T-cell line	Anti-inflammatory, Antioxidant	Anticancer, Cardiovascular protective, Nephroprotective	(Kawahara et al., 1999)
		Variecolin, Variecolol	Inhibit human chemokine receptor CCR5	Anti-inflammatory, Antioxidant. Pro-inflammatory	Anticancer, Cardiovascular protective, Hepatoprotective	(Yoganathan et al., 2004)
5	Triterpenoids	Ursolic acid	Inhibits NF-κ B activation, Decreases iNOS & COX-2 expressions, inhibit T cell proliferation	Immunomodulator, Anti-inflammatory, Anticancer, Antioxidant	Hepatoprotective, Antimicrobial, Antiviral, Cardiovascular protective	(Zeng et al., 2012)
		Betulinic acid	Block NF-κ B pathway	Immunomodulatory, Anti-inflammatory, Anticancer, Antioxidant	Antiviral, Cardiovascular protective, Neuroprotective, Hepatoprotective	(Rabi et al., 2008)
		Lupeol	Decreases proinflammatory cytokine TNF-α, IL-1β & IL-6	Immunomodulatory, Anti-inflammatory, Anticancer, Antioxidant	Antimicrobial, Antiviral, Cardiovascular protective, Hepatoprotective	(Li et al., 2021)

(*continued on next page*)

Table 1 (*continued*)

S. No	Class	Name of compound	Molecular Mechanism	Immunomodulatory Activities	Other Biological Activities	Reference
		Cealastrol	Decreases levels of chemokines & cytokines TNF-α IL-1β	Immunomodulatory, Anti-inflammatory, Anticancer, Antioxidant	Antimicrobial, Hepatoprotective, Cardiovascular protective, Neuroprotective	(Zhang et al., 2019)
		Corticosterone + escin glycosides	Decreases TNF-α, IL-1β, reduces NO synthase in LPS	Antioxidant, antimicrobial, Immunomodulator	Hepatoprotective, Cardiovascular protective, Neuroprotective	(Gallelli et al., 2021)
		QS-21 fraction glycoside	Increases immunogenicity level of polysaccharide, protein & glycoprotein, inhibit the stimulation of humoral & cell mediated immunities	Immunomodulator	Hepatoprotective, Cardiovascular protective	(Pifferi et al., 2021)
		Asiatic acid	Decreases NO production, inhibit production of pro-inflammatory cytokines of TNF-α, IL-6 & IL-1β	Anti-inflammatory, Anticancer, Antioxidant	Anticancer, Cardiovascular protective	(Yuyun et al., 2018)
		Madecassoside	Reduces IL-6, TNF-α levels, increases IL-10 levels	Anti-inflammatory Immunomodulator	Hepatoprotective, Cardiovascular protective, Neuroprotective	(Li et al., 2009)
		3β,6β-Dihydroxyolean-12-en-27-oic acid	Increases NK cells & cytotoxic T lymphocytes activity, increases production of IL-2 & anti-SRBC antibody	Anti-inflammatory	Hepatoprotective, Cardiovascular protective, Neuroprotective and Nephroprotective	(Deng et al., 2009)
		Spergulagenic acid	Inhibits cytokines production	Anti-inflammatory		(Zhang and An, 2007)

can be classified into three subclasses based on their structure; without a ring) monocyclic (with one ring) and bicyclic (with two rings). They can. Exist as unsaturated hydrocarbons or have functional groups attached to them such as alcohol, aldehyde or ketone. Fig. 3 showcases molecules of monoterpenes. These compounds have the ability to undergo oxidation and cyclization processes. Due, to their molecular weight many monoterpenes are found in essential oils. Whats interesting is that numerous monoterpenes display a range of activities, including antibacterial, anti inflammatory antioxidant, antispasmodic, hypoglycemic and analgesic effects(Sobral et al., 2014), (Fig. 2 and Table 1).

2.2.2. *Sesquiterpenoids ($C_{15}H_{24}$) chemical structures and functions*

Sesquiterpenoids belong to a group of compounds known for their structure consisting of 15 carbon atoms and 24 hydrogen atoms ($C_{15}H_{24}$). These compounds are more complex and larger compared to hemiterpenoids or monoterpenoids. They play vital roles in nature. A notable example is artemisinin an sesquiterpenoid derived from the sweet wormwood plant. The distinctive structure of contributes to its effectiveness against malaria. Another sesquiterpenoid, acid is found in root and is renowned for its calming and anxiety relieving effects. Apart from their uses sesquiterpenoids also act as natural defense mechanisms in plants by deterring herbivores and protecting against pathogens. Due to their chemical diversity and versatile functions sesquiterpenoids have become subjects of research in fields like pharmaceuticals, agriculture and ecological interactions. Their study contributes not to the world but also, to human wellbeing. (Perveen, 2021), (Fig. 2 and Table 1).

2.2.3. *Diterpenoids ($C_{20}H_{32}$) chemical structures and functions*

Diterpenoids contain a chemically heterogeneous group of substituents with four isoprene units and 20 carbon atoms. They are mainly classified into mono-, di-, tri-, tetra-, penta-, and macrocyclic frameworks. Diterpenoids are naturally found in polyoxygenated forms, often consisting of keto and hydroxy groups esterified by aliphatic and aromatic acids. Diterpenoids are organic compounds with a specific structure composed of 20 carbon atoms ($C_{20}H_{32}$), which arises from the combination of four isoprene units (C_5H_8). These compounds exhibit a remarkable diversity of chemical structures, often with complex arrangements of carbon and hydrogen atoms. This structural versatility enables them to serve a wide range of functions in the natural world. Diterpenoids play a crucial role in plant biology by acting as hormones, regulating processes like stem elongation, germination, and flowering. Furthermore, they contribute to plant defence mechanisms, deterring herbivores and protecting against pathogens. Some diterpenoids, such as paclitaxel (Taxol), possess valuable medicinal properties and are used in cancer treatments due to their ability to inhibit cancer cell growth. Beyond these roles, diterpenoids also participate in ecological interactions, influencing the relationships between various species and ecosystems. In summary, the structure of diterpenoids, characterized by their 20-carbon framework, underlies their diverse and vital functions in plant biology, defence, medicine, and ecology (Perveen, 2021), (Fig. 2 and Table 1) .

2.2.4. *Sesterterpenoids ($C_{25}H_{40}$) chemical structures and functions*

Sesterterpenoids are derived from five isoprene units and contain 25 carbon atoms. They are classified into mono-, bi-, tri-, tetra-, and macrocyclic frameworks. Sesterterpenoids have diverse structures, and they exhibit a range of biological activities. Sesterterpenoids, characterized by their unique structure composed of 29 carbon atoms ($C_{29}H_{46}O_2$), represent a less common yet intriguing class of natural organic compounds. Squalene, a linear, branched sesterterpenoid, serves as a precursor for sterol biosynthesis, including cholesterol, and also finds utility in the cosmetic and pharmaceutical industries. Bisabolol, a sesterterpenoid with a bicyclic structure, is known for its anti-inflammatory and skin-soothing properties, often included in skincare products. Sesterterpenoid quinone metabolites, characterized by complex, oxygenated structures, often act as natural products with antibiotic, antifungal, and antiparasitic properties, contributing to the defense mechanisms of their producers. Dendocarbin A, a sesterterpenoid with a tetracyclic structure, has been identified in marine organisms and demonstrates potential as an antifungal agent. Although sesterterpenoids may receive less attention than other terpenoid classes, their diverse structures and functions make them captivating subjects of research with potential applications in various fields (Evidente et al., 2015), (Fig. 2 and Table 1).

2.2.5. *Triterpenoids ($C_{30}H_{48}$) chemical structures and functions*

Triterpenoids, with their characteristic structure comprising 30 carbon atoms and 48 hydrogen atoms ($C_{30}H_{48}$), represent a diverse and significant class of natural organic compounds. These compounds are renowned for their structural complexity, composed of six isoprene units, and they serve a multitude of functions across the natural world. One well-known triterpenoid is squalene, which acts as a precursor for the biosynthesis of sterols, including cholesterol, and has applications in the cosmetic and pharmaceutical industries. Another example is

Table 2
Various extraction and purification techniques of terpenoids.

S. No	Extraction Method	Principle	Advantages	Disadvantages	Characteristics and Target Compounds	Limitation	References
1	Steam Distillation	Vaporization of compounds with steam	- Low temperature and short extraction time - Minimal solvent use	- Sensitive compounds may degrade - Limited yield for some plant materials	- Suitable for heat-sensitive terpenoids - Often used for essential oil extraction	Limited yield for some plant materials	(Zhang et al., 2018)
2	Supercritical Fluid Extraction (SFE)	Use of supercritical fluid (usually CO2)	- Selective extraction of terpenoids - Green solvent, no residue left in the extract	- High equipment and operating costs - Requires specialized equipment	- CO2 is commonly used as a green solvent - Targets various terpenoids with tunable temperature and pressure	Requires specialized equipment	(Najmi et al., 2022)
3	Microwave-Assisted Extraction (MAE)	Microwave radiation for extraction	- Short extraction time and high efficiency - Energy-saving process	- Need for specialized equipment and containers - Potential risk of overheating and degradation	- Enhanced extraction efficiency with microwaves - Limited solvent use with rapid heating and cooling	Potential risk of overheating and degradation	(Raphael and Kuttan, 2003)
4	Ultrasound-Assisted Extraction (UAE)	Ultrasound waves cause cavitation	- Enhanced mass transfer and extraction efficiency - Green solvent, reduced extraction time	- Possibility of sonochemical side reactions - Potential degradation of thermolabile compounds	- Targets a wide range of terpenoids with improved extraction rates - Reduced energy consumption and eco-friendly process	Potential degradation of thermolabile compounds	(Kapadia et al., 2022)
5	Pressurized Liquid Extraction (PLE)	Use of high pressure to enhance solvent's solubility	- Green solvent, reduced extraction time - Faster extraction compared to conventional methods	- Potential degradation of thermolabile compounds - High equipment and operating costs	- Reduced energy consumption and eco-friendly process - Suitable for high-throughput extraction of terpenoids	High equipment and operating costs	(Mustafa and Turner, 2011)
6	Solid Phase Extraction (SPE)	Selective adsorption of terpenoids on a solid phase	- High selectivity and purification capabilities - Minimal solvent use	- Relatively low extraction yields for some compounds - Complex sample preparation	- Used for selective isolation of terpenoids from complex mixtures - Suitable for trace-level analysis of terpenoids	Complex sample preparation	(Mustafa and Turner, 2011)
7	Countercurrent Extraction (CCC)	Utilizes biphasic solvent systems with countercurrent flow	- High extraction efficiency and selectivity - Reduced solvent consumption - Reusable solvents	- Complex setup and operation - Requires skilled operators	- Used for large-scale extraction of terpenoids - Targets specific terpenoids for high purity extraction	Requires skilled operators	(Maryutina and Fedotov, 2019)
8	Hydrodistillation	Steam distillation with water	Suitable for heat-sensitive terpenoids	Relatively long extraction time	Effective for essential oil extraction	Limited yield for some plant materials	(Marčac et al., 2023)
9	Soxhlet Extraction	Continuous solvent extraction with reflux	Effective for complete extraction	Time-consuming process	Useful for non-polar terpenoids	High solvent consumption	(Zhang et al., 2018)
10	Enfleurage	Fat absorption of volatile compounds	Suitable for delicate flowers with low oil content	Time-consuming process	Commonly used for floral essential oils	Low yield and high labor intensity	(Soe et al., 2016)
11	Cold Pressing	Mechanical pressing of the plant material	Simple and cost-effective	Limited to certain oil-rich fruits (e.g., citrus)	Used for citrus essential oils and fixed oils	Not suitable for all terpenoids	(Chintkuntla, 2015)
12	Fractional Distillation	Separation based on boiling points	Effective for terpenoid mixtures	Requires precise temperature control	Used for separating and purifying terpenoids	Complex setup and operation	(Abubakar and Haque, 2020)
13	Liquid-Liquid Extraction	Solvent extraction with immiscible liquids	Suitable for selective extraction of specific terpenoids	Requires careful selection of solvents	- Used for targeted isolation and enrichment of terpenoids	Potential loss of volatile compounds	(Zhang et al., 2018)
14	Headspace Solid-Phase Microextraction (HS-SPME)	Absorption of volatiles on solid-phase fibers	Rapid and solvent-free extraction	Limited to volatile and semi-volatile terpenoids	Widely used for analyzing aroma compounds in plants	May not be suitable for non-volatile compounds	(Feng et al., 2022)
15	Simulated Moving Bed Chromatography (SMB)	Continuous chromatographic separation	High purification efficiency	Requires specialized equipment and expertise	Suitable for large-scale purification of terpenoids	- High operating costs	(Johannsen, 2007)
16	Carbon Dioxide Extraction (CDE)	Extraction using supercritical or liquid CO2	Green solvent, no residue left in the extract	High equipment and operating costs	Targets various terpenoids with tunable temperature and pressure	Requires specialized equipment	(Arumugham et al., 2021)

glycyrrhizin acid, found in licorice root, known for its sweet taste and medicinal properties, including anti-inflammatory effects. Triterpenoids are also present in the waxy coatings of leaves, providing protection against water loss and herbivores. Their structural diversity and functions encompass a wide array of roles, from contributing to human health to aiding in plant defence and ecological interactions, making them versatile and valuable compounds with applications in various fields (Evidente et al., 2015), (Fig. 2 and Table 1).

2.3. Monoterpenoids, sesquiterpeniods, diterpenoids, sesterpeniods and triterpenoids as main bioactive compound of essential compounds

The hydrophobic nature of monoterpenes and essential oils enables them to exert their influence on bacterial cells, leading to antimicrobial effects. Among the specific monoterpenes, α-terpineol stands out for its ability to enhance skin penetration and its insecticidal properties (Mahizan et al., 2019). Moreover, studies have demonstrated that monoterpenes exhibit chemopreventive and chemotherapeutic activities in mammary tumor models, suggesting a potential new class of therapeutic agents for cancer treatment. The essential oil of Melissa officinalis L. has shown promise in inhibiting the replication of herpes simplex virus type 2 (HSV-2), primarily due to the presence of citral and citronellal. Another notable monoterpene, linalool, found as a principal constituent in many essential oils, exhibits a wide array of biological activities, including antibacterial, antiplasmodial (anti-malaria), and antinociceptive (pain-relieving) effects in various animal models. The multifaceted and extensive therapeutic properties of monoterpenes and monoterpenoids make them highly intriguing subjects for further research and development. Their potential as natural remedies and pharmaceutical agents holds significant promise for advancing healthcare and wellness (Adorjan and Buchbauer, 2010).

2.4. Bioactive constituent of terpenoids present in essential oils

For centuries, natural compounds have been utilized in traditional medicine, whether in the form of extracts, resins, or essential oils. Among these, essential oils, extracted from aromatic plants, have captured the attention of researchers worldwide. However, the complex mixture of volatile substances present in essential oils has made it challenging to fully understand their potential biological activities, which could hold industrial significance (Sharifi-Rad et al., 2017). Essential oils are volatile substances that result from the secondary metabolism of aromatic plants, and their components typically have low molecular weights. Nevertheless, various natural factors, such as physiological variations, environmental conditions, geographic diversity, genetic factors, and plant evolution, can influence the chemical composition and yield of these oils. Due to their potential as biologically active agents, essential oils have garnered substantial interest in the pharmaceutical industry, leading to extensive research. Over the years, numerous pharmacological activities have been demonstrated for these volatile compounds, including antioxidant, anticancer, antiprotozoal, antimicrobial, anti-inflammatory, phytotoxic, and neuroprotective properties. The diverse range of potential medicinal applications makes essential oils a fascinating subject of study for researchers seeking to harness the therapeutic potential of natural compounds. As scientific investigations continue, these oils hold the promise of contributing to the development of new pharmaceutical products and treatments (Santana de Oliveira et al., 2023). Essential oils exhibit a diverse array of constituents, primarily falling into categories such as monoterpenes, sesquiterpenes, benzenoids, and phenylpropanoids. Notably, species belonging to the Amaranthaceae family are particularly rich in bioactive compounds that offer numerous health benefits to humans. Some of the main bioactive compounds found in these plants include α-terpinene, δ-3-carene, limonene, thymol, carvacrol, γ-terpinene, α-terpinolene, piperitone oxide, geraniol, α-pinene, β-pinene, iso-ascaridole, β-myrcene, α-ocimene, β-ocimene, citronellyl acetate, β-phellandrene, dihydroascaridole, trans-pinocarveol, carvone, piperitone, p-cymene, 4-carene, δ-3-carene, fenchone, linalool, menthone, nerol, β-pinene, pulegone, terpineol-4-ol, thujone, and iso-ascaridole. These bioactive compounds have been linked to a wide range of biological activities, including antibacterial, antiviral, anti-leishmanial (effective against the parasite causing leishmaniasis), antioxidant, and anticancer effects (Pérez Zamora et al., 2018). The extensive variety of beneficial compounds found in essential oils, particularly those from the Amaranthaceae family, offers promising opportunities for research and development in the field of natural medicine. Their potential therapeutic effects, especially in combating bacterial and viral infections, as well as their antioxidant and anticancer properties, present exciting possibilities for the development of new treatments and health-promoting products. Bioactive compounds are chemical constituents found in essential oils that have specific biological effects when they interact with living organisms. Essential oils are highly concentrated extracts obtained from various parts of plants, such as leaves, flowers, fruits, stems, and roots. These oils are rich in bioactive compounds, which are responsible for the unique aroma and potential therapeutic properties of each essential oil. The bioactive compounds in essential oils can vary significantly from one oil to another and are typically present in small quantities. Each compound contributes to the overall chemical profile of the oil and may have distinct effects on the human body, including physical and psychological benefits (Mohamed and Alotaibi, 2023).

2.5. Extraction and purification techniques of terpenoids

Extraction and purification techniques of terpenoids are essential processes for isolating these natural compounds from plant sources or other biological materials. Terpenoids encompass a diverse group of organic compounds, and their extraction and purification methods may vary based on their specific properties and the desired end product. An overview of common extraction and purification techniques for terpenoids (Table 2).

2.6. Extraction techniques

2.6.1. Steam distillation

Steam distillation is a widely used technique, especially for extracting essential oils from aromatic plants. The process involves passing steam through the plant material. The heat of the steam vaporizes the volatile terpenoids and other aromatic compounds within the plant. These vaporized compounds are then carried along with the steam. As the mixture is condensed, the steam and terpenoids return to a liquid state. The condensed liquid, known as the "hydrosol" or "essential oil," contains the desired terpenoids and aromatic compounds. This method is particularly effective for extracting essential oils from plants with aromatic properties, such as lavender, eucalyptus, or mint (Kumar Mahawer et al., 2022).

2.6.2. Solvent extraction

Solvent extraction is another common approach for isolating terpenoids. In this method, non-polar or polar solvents like hexane, ethyl acetate, ethanol, or water are used to dissolve the terpenoids from the plant material. The choice of solvent depends on the polarity of the terpenoids to be extracted. Non-polar solvents are suitable for less polar terpenoids like diterpenoids and sterols, while polar solvents are used for highly oxygenated triterpenoids, glycosylated terpenoids, and sterols (Jiang et al., 2016). Apart from these traditional methods, there is an increasing focus on developing more sustainable and efficient extraction techniques. Supercritical fluid extraction (SFE), ultrasound-assisted extraction (UAE), and microwave-assisted extraction (MAE) are some of the emerging methods. SFE employs supercritical CO2 as a green solvent and offers high selectivity. UAE and MAE utilize ultrasound or microwave energy to enhance extraction efficiency, significantly reducing extraction times (Jha and Sit, 2023).

2.6.3. Supercritical fluid extraction (SFE)

In Supercritical Fluid Extraction (SFE), the supercritical fluid of choice is carbon dioxide (CO2). This technique is favored for its environmentally friendly characteristics and its efficiency in extracting a broad spectrum of compounds, including terpenoids (López-Hortas et al., 2022). CO_2, in particular, becomes supercritical at relatively low pressures and moderate temperatures, which makes it a practical choice for SFE. In this supercritical state, CO_2 combines the desirable properties of both a gas and a liquid. It exhibits gas-like diffusion capabilities, allowing it to permeate plant materials efficiently, and liquid-like density, which facilitates the dissolution of terpenoids. The SFE process typically involves an extraction chamber where the supercritical CO_2 is maintained under controlled pressure and temperature conditions. This supercritical CO_2 is then introduced to the plant material, enabling it to dissolve and carry away the terpenoids. Subsequently, the mixture is directed to a separator, where adjustments in pressure and temperature prompt the CO_2 to revert to its gaseous state. During this phase change, the terpenoids are left behind, isolated and pure. Importantly, there are no solvent residues left in the final extract. This method is often referred to as "green" due to several key advantages. Firstly, CO_2 is non-toxic, non-flammable, and readily available, making it a safe and sustainable choice for extraction. Moreover, the ability to fine-tune pressure and temperature allows for excellent selectivity, making it possible to target specific compounds. SFE is also recognized for its efficiency, as it typically results in shorter extraction times when compared to traditional methods. These attributes have made SFE an attractive option for a wide range of applications, including the extraction of terpenoids. In summary, Supercritical Fluid Extraction with CO_2 stands out as an environmentally conscious and highly efficient method for extracting terpenoids and other compounds, promising a greener and cleaner future for natural product isolation (Prasad et al., 2023).

2.6.4. Ultrasound-assisted extraction (UAE)

Ultrasound-Assisted Extraction (UAE) is a technique that leverages the power of ultrasound waves to optimize the extraction of terpenoids and other valuable compounds from plant materials. This method is characterized by its efficiency and shorter extraction times, making it an attractive choice in the field of terpenoid extraction (Kumar et al., 2021). UAE's efficiency is attributed to its ability to disrupt plant cell walls. The ultrasonic waves, generated by a probe placed in the extraction medium, create alternating high-pressure and low-pressure cycles. These pressure fluctuations induce the formation and collapse of tiny bubbles in the liquid, a phenomenon known as cavitation. During cavitation, the violent implosion of these bubbles generates intense local heat and pressure, which results in the mechanical disruption of plant cells. This disruption allows for the release of terpenoids trapped within the plant matrix, making them more accessible for extraction (Mukherjee, 2019). While UAE is used for various applications, it is particularly well-suited for the extraction of terpenoids due to their often delicate and volatile nature. The rapid and efficient extraction provided by UAE can yield high-quality terpenoid extracts with minimal degradation or alteration of the compounds. UAE has the potential to enhance the productivity of the extraction process, offering researchers and industry professionals a more efficient and time-saving approach to obtain terpenoid compounds from natural sources (Zhang et al., 2018).

2.6.5. Microwave-assisted extraction (MAE)

Microwave-Assisted Extraction (MAE) is an extraction method that capitalizes on microwave energy to expedite the extraction of terpenoids and other compounds from plant materials. This technique is renowned for its rapid extraction rates and efficiency, offering a valuable approach to terpenoid extraction (López-Salazar et al., 2023). In MAE, microwave energy is harnessed to heat both the solvent and the plant material concurrently. The microwave radiation agitates the molecules in the solvent and plant matrix, leading to increased kinetic energy, which accelerates the extraction process. The heat generated also helps to disrupt the cell walls of the plant material, facilitating the release of terpenoids into the solvent (Hamid Nour et al., 2021). The advantages of MAE in terpenoid extraction are significant. Its rapid extraction rates substantially reduce the time needed to obtain terpenoid extracts compared to traditional methods. This speed is advantageous in preserving the integrity of terpenoid compounds, which can be sensitive to prolonged exposure to heat or solvents (Xu et al., 2017). The efficiency of MAE is particularly beneficial when working with terpenoids due to their often volatile and delicate nature. The accelerated extraction process minimizes the potential for degradation or alteration of terpenoid compounds, resulting in higher-quality extracts (Lazarjani et al., 2021). While MAE finds applications in various fields, including food and pharmaceuticals, it offers a compelling solution for terpenoid extraction from plant sources. This approach not only streamlines the extraction process but also contributes to the productivity of researchers and industry professionals working with terpenoid compounds (Jiang et al., 2016).

2.7. Purification techniques

2.7.1. Column chromatography

Column chromatography is a chromatographic technique widely employed in the isolation and purification of terpenoids and other organic compounds. It relies on the differential affinities of terpenoids for a solid stationary phase, facilitating their separation. This method is valuable for researchers aiming to obtain purified terpenoid extracts from complex mixtures (Jiang et al., 2016). In column chromatography, a vertical glass column is packed with a solid stationary phase, often silica gel or alumina. The mixture containing terpenoids is carefully applied to the top of the column. As a solvent is continuously introduced into the column, it percolates through the stationary phase, carrying the terpenoids along with it. During this process, terpenoids with varying affinities for the stationary phase separate (Handa et al., 2008). The concept underlying this separation lies in the differing interactions between the terpenoids and the stationary phase. Compounds that have a stronger affinity for the stationary phase will interact more and, consequently, move more slowly through the column. In contrast, terpenoids with a weaker affinity for the stationary phase will progress more rapidly, resulting in separation based on these varying affinities. The column chromatography in terpenoid isolation are evident. It allows for the separation of terpenoids from complex mixtures, and the elution process can be adjusted to optimize the purification of specific terpenoid compounds (Frolova et al., 2020).

2.7.2. Thin-layer chromatography (TLC)

Thin-Layer Chromatography (TLC) is a chromatographic method widely utilized for the separation and visualization of terpenoids and other compounds. This technique is based on the principle of differential migration, where terpenoids within a sample are separated on a thin layer of adsorbent material applied to a plate. The process begins by applying a small amount of the sample, often in the form of a concentrated solution or extract, as a spot or line near the base of the TLC plate. The TLC plate is typically a glass or plastic sheet coated with a thin layer of adsorbent material, commonly silica gel or aluminum oxide. This adsorbent layer serves as the stationary phase in the chromatographic process. Once the sample is spotted on the plate, it is placed in a developing chamber containing a solvent. As the solvent migrates up the plate through capillary action, it carries the terpenoids within the sample along with it. The separation of terpenoids occurs as they interact with the adsorbent material in the thin layer. Terpenoids with different affinities for the adsorbent will move at varying rates, leading to their distinct separation along the plate (WUTSQA et al., 2021).

For terpenoid analysis in TLC, a variety of solvent systems can be employed based on the specific terpenoids being studied. Some commonly used solvent systems include:

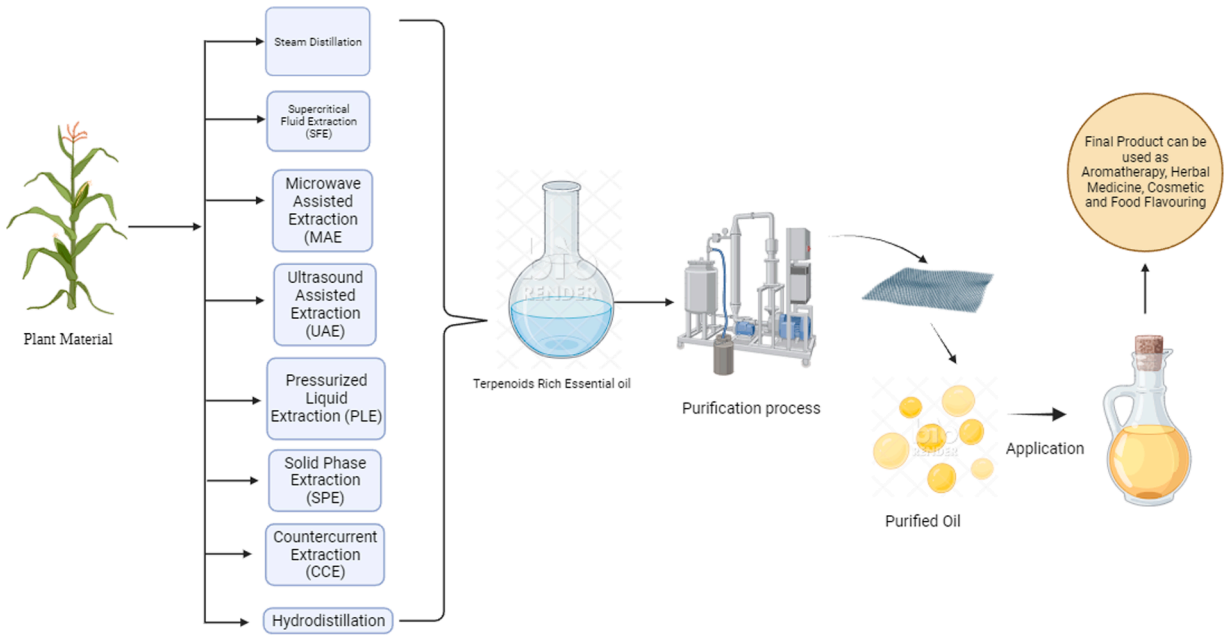

Fig. 3. Extraction and Purification Techniques of Terpenoids

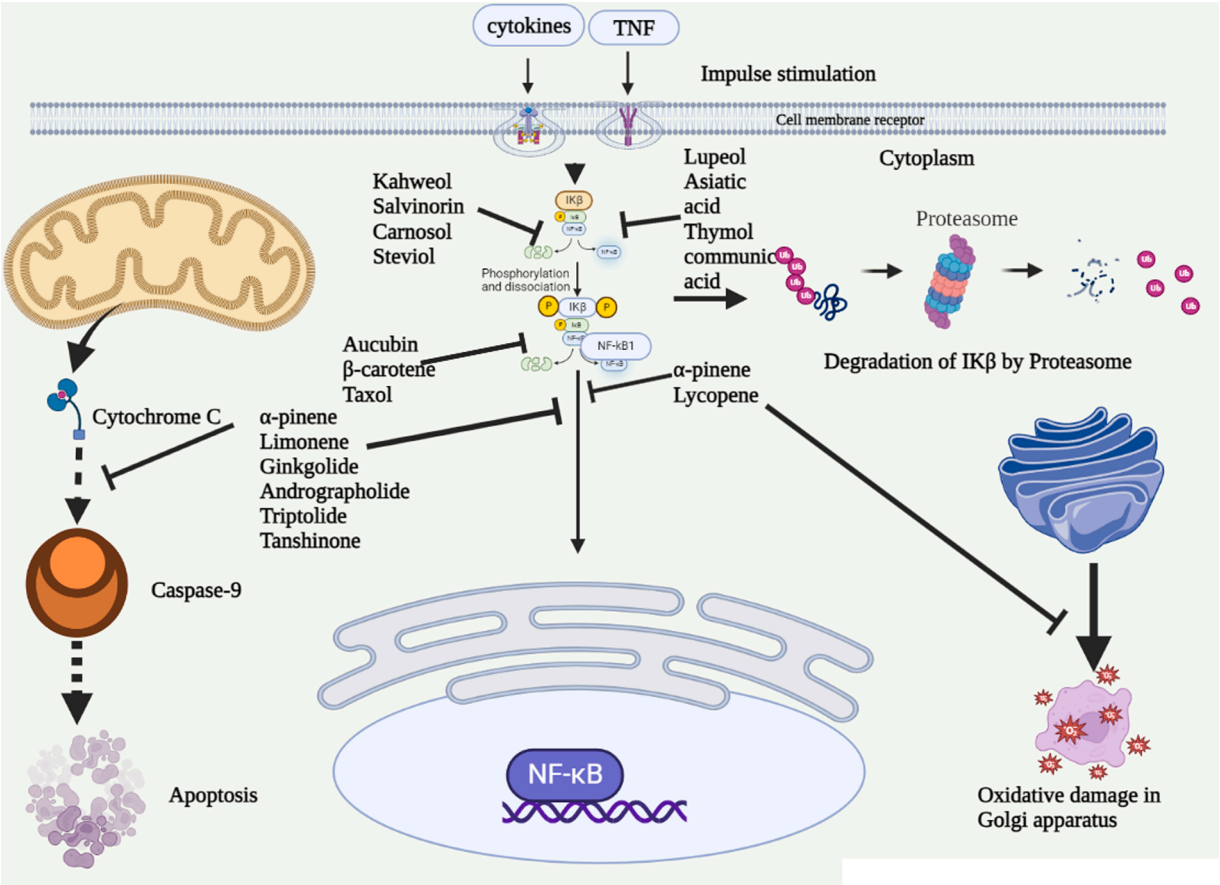

Fig. 4. Multi-Mechanism approaches of terpenoid to inhibit TNF and cytokinesis.

(A). Ethyl Acetate-Hexane: This system is effective for separating a wide range of terpenoids, as it offers a good balance between polarity and non-polarity. The ratio of ethyl acetate to hexane can be adjusted to fine-tune the separation.

(B). Chloroform-Methanol: This system is suitable for terpenoids with higher polarity. Chloroform serves as the non-polar component, while methanol provides the polar aspect. The ratio can be optimized based on the polarity of the terpenoids of interest (Kowalska and Sajewicz, 2022).

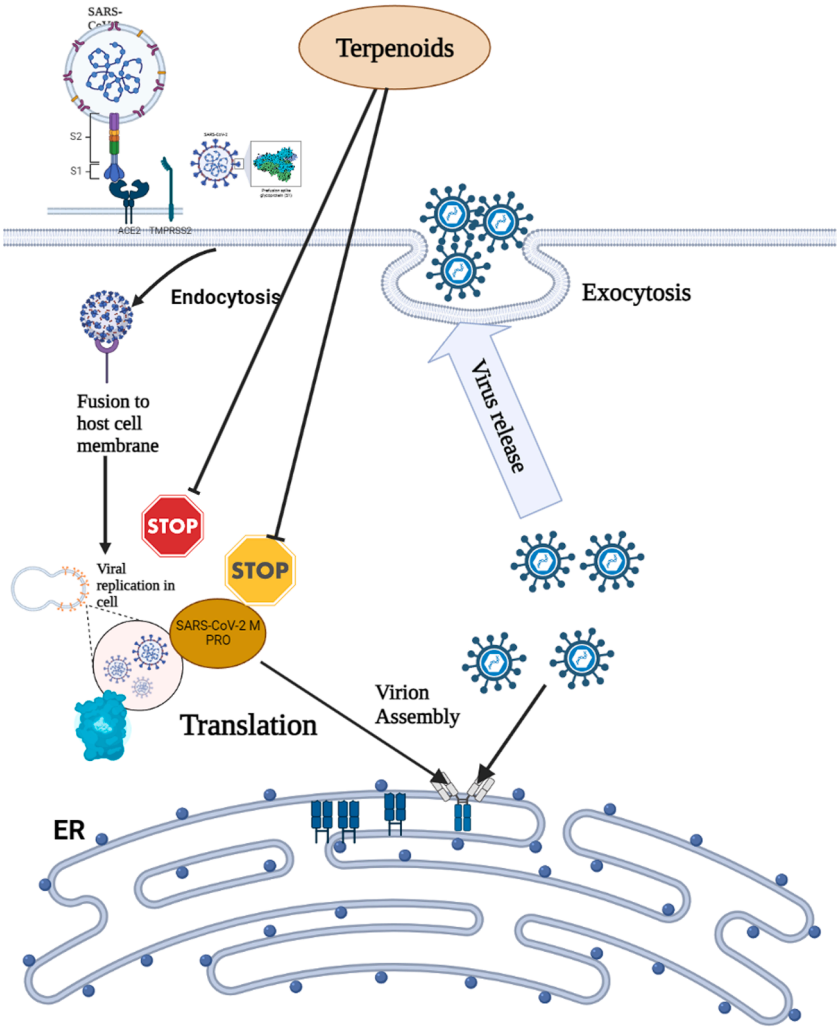

Fig. 5. Terpenoids are predicted to block the viral part that is M^{PRO} required for replication, prevention, and treatment of SARS-CoV-2.

2.7.2.1. Mobile phase ratios. The ratio of the mobile phase components in a solvent system is critical for achieving the desired separation in TLC. The choice of the ratio depends on the polarity of the terpenoids and the selectivity required. Here are some examples: In an ethyl acetate-hexane system, a common starting ratio is 1:1. This ratio can be adjusted to make the mobile phase more polar (by increasing ethyl acetate) or more non-polar (by increasing hexane) as needed for specific terpenoid separation. In a chloroform-methanol system, an initial ratio of 9:1 (chloroform:methanol) is often used. Again, this ratio can be modified to optimize the separation of terpenoids with varying polarities (Skalicka-Woźniak and Garrard, 2014).

2.7.3. High-performance liquid chromatography (HPLC)

High-Performance Liquid Chromatography (HPLC) is a sophisticated analytical technique that finds extensive application in the precise analysis of terpenoids, offering valuable scientific insights. Terpenoids, with their diverse chemical structures and biological activities, present a complex mix of compounds within natural extracts. HPLC serves as a scientific beacon, providing in-depth information about terpenoid composition and quality. In the context of terpenoids, HPLC is employed to separate and quantify these compounds based on their individual chemical properties. The separation process hinges on the interaction between the terpenoids and the stationary phase within the chromatographic column. This interaction leads to variations in elution times, allowing for the distinct separation of terpenoids within a mixture. The scientific merits of HPLC in terpenoid analysis are manifold. It delivers high precision and accuracy, enabling the differentiation of terpenoids with similar structures. This capability is crucial for identifying specific terpenoid compounds within a complex matrix, shedding light on their presence and concentration. Moreover, HPLC is known for its sensitivity, making it possible to detect even trace amounts of terpenoids (Handa et al., 2008). In terpenoid analysis, the choice of column is crucial for achieving optimal separation and resolution. Silica-based reversed--phase columns are commonly preferred. Columns with C18 (octadecylsilane) stationary phases are particularly well-suited for terpenoids due to their selectivity and compatibility with a wide range of compounds (Žuvela et al., 2019).

For terpenoid analysis, a UV-Vis (Ultraviolet-Visible) detector is often employed. UV detection is effective because many terpenoids absorb UV light, allowing for their quantification. Additionally, the use of a refractive index detector (RID) can be beneficial in cases where UV detection alone might not provide adequate sensitivity or selectivity (Žuvela et al., 2019). The adaptability of HPLC is especially advantageous for terpenoid research. Various column types, detectors, and mobile phases can be tailored to the specific properties of terpenoids. This flexibility empowers researchers to delve deeply into terpenoid composition, elucidating their chemical characteristics and potential roles in biological activities. The application of HPLC in terpenoid analysis is a cornerstone of scientific research within this field. It enables the investigation of terpenoid profiles in natural products, the evaluation of terpenoid-rich essential oils, and the verification of terpenoid purity in pharmaceuticals. Furthermore, HPLC aids in monitoring the

Table 3
Pharmacological roles of terpenoid compounds.

Activity	Type of terpenoid	Mode of action	Pharmacological Effects	Potential Applications	Toxicity	References
Antiplasmodial Activity	Limonene Pinene caryophyllene	Terpenes act similarly to antimalarial medication chloroquine, attaching to the hemin portion of diseased erythrocytes.	Antimalarial, Anti-inflammatory	Malaria treatment	Low toxicity	(Cox-Georgian et al., 2019)
Antiviral Activity	Carvone, carveol limonene, alphaand beta-pinene, caryophylene, camphor, beta-ocimene	Monoterpenes trigger cell cycle arrest (G0/G1 phase), suggesting a combination may be more effective than individual monoterpene	Antiviral, Antimicrobial	Antiviral agent, Natural	Low toxicity	(Baron, 2018)
Anticancer	Thymoquinone alloocimene, camphor, beta-myrcene, pinene, alpha- and gamma-thujaplicin, terpinene, thymohydroquinone, carvone, camphene, and cymene	Reducing the activity of cyclin D1 in metastatic breast cancer. This resulted in cell cycle arrest and reduced cancer cell growth in women with initial periods breast cancer.	Terpenoids reduce cyclin D1 activity in metastatic breast cancer, leading to cell cycle arrest and reduced cancer cell growth.lo	Anticancer, Apoptosis	Cancer treatment	(Yang et al., 2020)
Antidiabetic	Myrcene	lowers glucose levels and enhances glucose utilization in diabetes rats. It activates alpha-adrenoreceptors, leading to increased production of opioid peptide beta-endomorphin	Antidiabetic, Glucose control	Diabetes management	Low toxicity	(Habtemariam, 2018)
Antidepressant	Linalool and Beta-pinene, sesquiterpenes, beta-caryophyllene	Terpenoids regulate serotonin pathways (5HT1A receptors), crucial for coping with stress. They also interact with adrenergic receptors during stress.	Antidepressant, Anxiolytic	Mental health support, Anti-stress, Aromatherapy	Low toxicity	(Cox-Georgian et al., 2019)
Antitumor Activity	Perilly alcohol, Geranicol, Costunolide,Artemisinin, Paclitaxel	Terpenoids block MCF-7 breast cancer cell cycle, slowing tumor growth. Geraniol elevates cyclin p27Kip1 levels and reduces cyclin D1, cyclin-dependent kinase 4, cyclin E, and cyclin A	Anticancer, Apoptosis	Cancer treatment	Low toxicity	(Baron, 2018)
Anti-Inflammatory Activity	Triptolide, Tripterine, Triptonide, Ginsenoside	Terpenoids inhibit LPS-induced nitric oxide (NO) generation and possess anti-inflammatory properties	Anti-inflammatory, Immunomodulatory	Inflammation management, Antioxidant, Immune support	Moderate toxicity	Yang et al., 2020)
Antibacterial Activity	Limonene, Geranialdehyde, Sabinol, Carvone, Oleanolic acid	Terpenoids display antibacterial action with minimum bacterial concentrations (MBCs) between 25 and 75 g/mL	Antibacterial, Antimicrobial, Food preservation	Natural antibiotics, Pest pylori, inhibiting motility and flagella development	Low toxicity	Yang et al., 2020)
Cardio-protective effect	Tanshinone IIA, Ginsenoside,	Terpenoids halt atherosclerosis, cardiac injury, and hypertension. Tanshinone IIA stabilizes atherosclerotic plaque and inhibits LDL oxidation	Cardiovascular protection, Anti-oxidative, Heart health support,	Cardioprotective properties, Anti-inflammatory, Atherosclerosis prevention,	Low toxicity	(Su et al., 2019)
Antioxidant effect	Ginsenoside	Its regulates the production of regulatory elements in the cell cycle, protects cardiomyocytes from oxidative injury caused by both internal and external oxidants, and subsequently exhibits its antiaging actions.				(Yang et al., 2020)

dynamic changes in terpenoid composition during plant development and in response to environmental factors (Lü et al., 2020).

2.7.4. Crystallization

Terpenoids can be purified through crystallization by cooling or evaporating a solvent, causing the compound to form crystals. This method can be highly effective for achieving high purity. Crystallization is a critical chemical unit operation commonly used in the biological separation of terpenoids. It is highly effective for obtaining pure and solid terpenoid compounds from relatively impure solutions in a single step. To efficiently produce high-bioactive minor ginsenosides C-K or F2 during the separation of ginsenosides, Xiao et al. isolated an Aspergillus niger strain, referred to as g.848. This strain contains ginsenosides typ1-I, which can convert PPD-ginsenosides into C-K. The process involves fermentation, vacuum concentration, macroporous resin adsorption, ethanol elution, and subsequent recrystallization with methanol. Through these steps, the raw product C-K is obtained, and its purity is enhanced from 85% to 98% (Xiao et al., 2019).Over the past 40 years, researchers have dedicated significant efforts to research and develop crystallization technology to meet the requirements of industrial production. As a result, various industrial crystallization devices have been developed and applied in practical settings. These include vacuum crystallizers, FC continuous crystallizers, DTB crystallizers, and more. The advancements in crystallization technology have played a crucial

Table 4A
Absorption, distribution, metabolism, excretion, and toxicity (ADMET) characteristics (1) Thymol, (2) Carvacrol, (3) Citral, (4) α-Pinene, (5) D-Limonene, (6) Linalool, (7) Linalyl acetate, (8) Cineole or 1,8-Cineole, (9) Thymoquinone & Thymohydroquinone, (10) Borneol, 1-borneol, 1-bornyl acetate, (11) Geraniol, (12) Perillic acid, (13) β- Myrcene.

Monoterpenoid	01	02	03	04	05	06	07	08	09	10	11	12	13
Drug-Likeness													
Lipinsk	+	+	+	+	+	+	+	+	+	+	+	+	+
Bioavailability score	0.55	0.55	0.55	0.55	0.55	0.56	0.56	0.55	0.55	0.55	0.55	0.85	0.55
Absorption													
Water solubility	-2.062	-2.043	-3.377	1.504	-3.733	-3.568	-2.64	-2.749	-1.594	-3.015	-2.866	-0.55	-4.481
Caco2 permeability	1.466	1.52	1.504	0.40	1.38	1.401	1.492	1.172	1.344	2.086	1.49	1.21	1.405
Intestinal absorption (human)	92.154	97.80	95.317	100	96.041	95.898	92.943	95.934	98.531	2.086	92.788	90.91	95.393
Skin Permeability	-2.055	-1.64	-2.413	-2.81	-1.827	-1.721	-1.7	-1.914	-2.533	-2.262	-1.511	-3.38	-1.058
P-glycoprotein substrate	-	-	-	+	-	+	-	+	-	-	-	+	-
P-glycoprotein I inhibitor	-	-	-	+	-	-	-	-	-	-	-	-	-
P-glycoprotein II inhibitor	-	-	-	-	-	-	-	-	-	-	-	-	-
Distribution													
VDss (human)	0.441	0.451	0.166	0.35	0.667	0.396	0.155	0.047	-0.034	0.313	0.13	0.17	0.368
Fraction unbound (human)	0.249	0.31	0.42	0.14	0.425	0.48	0.48	0.446	0.535	0.406	0.26	0.447	0.386
BBB permeability	0.403	0.383	0.626	-1.32	0.791	0.732	0.611	0.554	0.372	0.565	0.15	0.606	0.786
CNS permeability	-1.487	-1.555	-1.986	-3.87	-2.201	2.37	-2.329	-2.43	-2.227	-2.419	-1.98	-2.159	-1.912
Metabolism													
CYP2D6 substrate	-	-	-	-	-	-	-	-	-	-	-	-	-
CYP3A4 substrate	-	-	-	+	-	-	-	-	-	-	-	-	-
CYP1A2 inhibitor	+	+	-	-	-	-	-	+	-	-	+	-	-
CYP2C19 inhibitor	-	-	-	-	-	-	-	-	-	-	-	-	-
CYP2C9 inhibitor	-	-	-	-	-	-	-	-	-	-	-	-	-
CYP2D6 inhibitor	-	-	-	-	-	-	-	-	-	-	-	-	-
CYP3A4 inhibitor	-	-	-	-	-	-	-	-	-	-	-	-	-
Excretion													
Total clearance	0.211	0.207	0.376	0.150	0.043	0.213	0.446	1.075	0.225	1.029	0.55	0.437	0.438
Renal OCT2 substrate	-	-	-	-	-	-	-	-	-	-	-	-	-
Toxicity (Compound Number)													
AMES toxicity	-	-	-	-	-	-	-	-	-	-	-	-	-
Hepatotoxicity	+	+	-	+	-	-	-	-	+	-	-	-	-
hERG I inhibitors	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin Sensitization	+	-	-	-	-	-	-	-	-	-	-	-	-
Oral Rat Acute Toxicity (LD50)	2.347	2.251	1.815	4.01	1.77	1.88	1.713	1.932	1.68	1.994	2.28	1.636	1.683
Oral Rat Chronic Toxicity (LOAEL)	2.266	2.30	2.133	1.70	2.262	2.336	2.017	2.05	2.443	1.87	1.30	2.03	2.415

+ Sign signifies Yes, - Sign Signifies No

role in improving the efficiency and purity of product isolation for industrial applications (Chen et al., 2021). The choice of extraction and purification methods depends on the specific terpenoids of interest and the characteristics of the source material. Furthermore, researchers are continually developing and optimizing these techniques to improve efficiency, purity, and sustainability in the extraction and purification of terpenoids (Fig. 3**).**

2.8. Terpenoids' role in enhancing the human immune system

In recent years, there has been a growing body of research highlighting the importance of terpenes and terpenoids in supporting human health. These bioactive compounds, composed of several isoprene units, form the largest class of organic compounds found in the essential oils (EOs) of various plants. Their versatile nature enables them to play a significant role in treating various diseases, as evidenced by numerous in vitro and in vivo studies where they have been explored as potential anticancer agents, antimicrobial agents, anti-inflammatory agents, antioxidants, antiallergic agents, neuroprotective agents, anti-aggregators, anticoagulants, sedatives, and analgesics (Fig. 4**).**

The efficacy of terpenes and terpenoids in promoting health stems from the activity of different subclasses such as monoterpenes, sesquiterpenes, diterpenes, triterpenes, tetraterpenes, and glycoside compounds (Bhardwaj et al., 2020). Moreover, the presence of terpenes and terpenoids in nutritional and health products has garnered significant attention. They serve as valuable sources of essential vitamins, including vitamins A, E, K, and coenzyme Q10. Additionally, carotenoid and tocopherol compounds within this group play crucial roles as vitamins, particularly in animals, including humans (Gutiérrez-Del-río et al., 2021). The practical applications of terpenes extend to various industries, making them an integral part of everyday human life and health. These compounds find use in pharmaceuticals, nutraceuticals, food and beverage products, cosmetics, perfumes, synthetic chemicals, aroma and flavor additives, rubber products, and even the biofuel industry. Their versatility and beneficial properties make them sought-after ingredients in a wide range of products and industries. Overall, the ongoing research and increasing utilization of terpenes and terpenoids demonstrate their significance in supporting human health and their potential for further contributions to various aspects of our daily lives (Fan et al., 2023). As science continues to advance, we can anticipate even more exciting discoveries and applications for these natural compounds.

2.8.1. Antioxidant activity: implications for health and disease

Certain essential oils (EOs) play a crucial role in reducing oxidative stress and are often utilized to prevent various chronic diseases. Chamazulene, derived from the EOs of Matricaria chamomilla (chamomile), is a bicyclic sesquiterpene known for its beneficial effects. In a study by Querio et al. (2018), chamazulene was found to effectively balance the levels of reactive oxygen species (ROS) in bovine aortic endothelial cells-1 (BAECs). These cells experienced an increase in ROS levels due to exposure to high glucose and H2O2, but chamazulene treatment helped restore their balance, highlighting its potential as an antioxidant agent. Another valuable compound is ursolic acid, a pentacyclic triterpenoid carboxylic acid isolated from Entada abyssinica. Ursolic acid has been shown to possess antioxidant activity, as demonstrated by its IC50 values of 1.43 ± 0.080 μg/ml, 2.87 ± 1.19 μg/ml, and 7.04 ± 1.29 μg/ml in the FRAP, DPPH, and ABTS methods, respectively (Masyita et al., 2022). To assess antioxidant activity, researchers often use the FRAP, DPPH, and ABTS methods, which involve radical compounds and

Table 4B
Absorption, distribution, metabolism, excretion, and toxicity (ADMET) characteristics (1) Turmerone, (2) Curcumolide, (3) Farnesol, (4) Nerolidol, (5) Zerumbone, (6) Valerenic acid, (7) Ziniolide, (8) α-Bisabolol (9) Matricine, (10) Curdione (11) Germacrone.

Sesquiterpenoids	01	02	03	04	05	06	07	08	09	10	11
Drug-Likeness											
Lipinsk	+	+	+	+	+	+	+	+	+	+	+
Bioavailability score	0.55	0.55	0.55	0.55	0.55	0.56	0.56	0.55	0.55	0.55	0.55
Absorption											
Water solubility	-4.556	-3.071	-5.393	-5.200	-4.027	-3.649	-3.626	-4.412	-3.092	-3.431	-4.298
Caco2 permeability	-4.556	1.374	1.495	1.498	1.432	1.606	1.587	1.500	1.170	1.290	1.434
Intestinal absorption (human)	-4.556	98.77	91.531	91.673	95.781	96.569	1.587	92.096	97.418	97.689	95.515
Skin Permeability	-1.735	-3.026	-1.514	91.673	-2.060	-2.699	-2.537	-1.718	-3.731	-2.338	-1.922
P-glycoprotein substrate	-	-	-	-	-	-	-	-	-	-	-
P-glycoprotein I inhibitor	-	-	-	-	-	-	-	-	-	-	-
P-glycoprotein II inhibitor	-	-	-	-	-	-	-	-	-	-	-
Distribution											
VDss (human)	0.48	0.229	0.36	0.37	0.279	-0.554	0.437	0.417	0.011	0.093	0.292
Fraction unbound (human)	0.12	0.392	0.206	0.231	0.395	0.232	0.329	0.32	0.403	0.346	0.356
BBB permeability	0.516	0.092	0.66	0.655	0.522	0.232	0.329	0.601	-0.241	0.398	0.526
CNS permeability	-1.747	-2.727	-1.933	-2.09	-2.647	-2.144	-2.49	-2.521	-2.929	0.398	-2.48
Metabolism											
CYP2D6 substrate	-	-	-	-	-	-	-	-	-	-	-
CYP3A4 substrate	-	-	-	+	-	-	-	-	-	+	-
CYP1A2 inhibitor	+	+	-	-	-	-	-	+	-	-	-
CYP2C19 inhibitor	-	-	-	-	-	-	-	-	-	-	-
CYP2C9 inhibitor	-	-	-	-	-	-	-	-	-	-	-
CYP2D6 inhibitor	-	-	-	-	-	-	-	-	-	-	-
CYP3A4 inhibitor	-	-	-	-	-	-	-	-	-	-	-
Excretion											
Total clearance	0.309	0.193	1.754	1.739	1.314	1.191	0.693	0.225	1.075	1.355	1.416
Renal OCT2 substrate	-	-	-	-	-	-	-	-	-	-	-
Toxicity (Compound Number)											
AMES toxicity	-	-	-	-	-	-	-	-	-	-	-
Hepatotoxicity	+	+	-	+	-	-	-	-	+	-	-
hERG I inhibitors	-	-	-	-	-	-	-	-	-	-	-
Skin Sensitization	+	-	-	-	-	-	-	-	-	-	-
Oral Rat Acute Toxicity (LD50)	1.972	1.92	1.558	1.597	1.802	1.734	1.813	1.68	2.356	1.778	1.768
Oral Rat Chronic Toxicity (LOAEL)	1.225	1.60	1.208	1.178	1.178	2.28	1.739	2.443	1.082	1.934	1.218

+ Sign signifies Yes, - Sign Signifies No

color changes during the evaluation process. In the DPPH (2,2-diphenyl-1-picrylhydrazyl) method, the DPPH radical undergoes a color change from purple to pale yellow when its free electrons bind to hydrogen atoms of antioxidant compounds, resulting in the formation of a non-radical compound called diphenylpicrylhydrazine. In the ABTS (2, 2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)) method, the solution changes its color from blue or green to colorless as antioxidant compounds accept proton donors, leading to the neutralization of the ABTS radical cation. In the FRAP (ferric reducing antioxidant power) method, the solution changes color from yellow to blue when antioxidant compounds facilitate the electron transfer from ferri-tripyridyl-triazine (Fe(III)TPTZ) to ferro-tripyridyl-triazine (Fe(II) TPTZ). These methods offer valuable insights into the antioxidant capacity of various compounds, including those found in essential oils. Chamazulene and ursolic acid's antioxidant properties make them promising candidates for potential therapeutic applications in mitigating oxidative stress and related chronic diseases. Their natural origin from plant sources adds to their appeal as potential agents for promoting human health (Shahidi and Zhong, 2015).

2.8.2. *Proinflammatory activity: mechanisms and therapeutic potential*

In recent years, there has been growing recognition of the physiological importance of terpenes and terpenoids in alleviating various inflammatory symptoms. These compounds have demonstrated the ability to inhibit multiple pathological steps in the inflammatory process, as highlighted by (Del Prado-Audelo et al., 2021). Inflammation is a vital protective response of the body to foreign substances, often resulting from microbial infections or tissue damage. However, when inflammatory responses become dysregulated, they can lead to acute and chronic inflammatory diseases, causing excessive or prolonged tissue damage by Macrophages, which are key immune cells, play a central role in various immune pathological phenomena during inflammation. They are responsible for the overproduction of pro-inflammatory cytokines and inflammatory mediators, including interleukin-1β (IL-1β), IL-6, tumor necrosis factor-alpha (TNF-α), nitric oxide (NO) synthesized by inducible NO synthase (iNOS), and prostaglandin E2 (PGE-2) synthesized by cyclooxygenase-2 (COX-2). The central transcription factor, nuclear-κB (NF-κB), is also crucial in regulating the expression of pro-inflammatory genes during inflammation (Chen et al., 2018). Moreover, cellular processes such as oxidative stress and autophagy play essential roles in inflammation. Reactive oxygen species (ROS), which originate from various sources, including mitochondria, mediate increased leukocyte migration and junctional permeability through various signaling mechanisms. Additionally, a recent study demonstrated that ROS directly interferes with NF-κB signals, thus regulating the release of IL-1β (Kiran et al., 2021). These findings shed light on the complex mechanisms underlying inflammation and the potential of terpenes and terpenoids to modulate these processes positively. Understanding the interactions between these natural compounds and the inflammatory pathways holds promise for developing new therapeutic strategies to manage inflammatory diseases effectively. These studies mentioned show promising results for the potential use of certain terpenes and terpenoids in the treatment of inflammatory conditions and the development of new anti-inflammatory drugs. (+)-α-terpineol, (−)-β-pinene, and (+)-α-pinene have been found to reduce the expression of genes associated with inflammation (IL-4 and IL-13) and the secretion of β-hexosaminidase in RBL-2H3 cells stimulated by LPS. These findings suggest that these compounds may have anti-inflammatory properties and could be explored further as potential therapeutic agents for managing inflammation. Another terpene, borneol, has shown interesting effects in the treatment of cerulein-induced acute pancreatitis. It has been reported to significantly increase the activation of

Table 4C
Absorption, distribution, metabolism, excretion, and toxicity (ADMET) characteristics (1) Andrographolide, (2) Ginkgolides, (3) Triptolide, (4) Tanshinone, (5) Tanshinone IIA, (6) Carnosol, (7) Salvinorin A, (8) Steviol, (9) Stevioside, (10) Austroinulin, (11) Communic acid, (12) Copallic acid, (13) Kahweol.

Diterpenoids	01	02	03	04	05	06	07	08	09	10	11	12	13
Drug-Likeness													
Lipinsk	+	+	+	+	+	+	+	+	+	+	+	+	+
Bioavailability score	0.55	0.55	0.55	0.55	0.55	0.56	0.56	0.55	0.55	0.55	0.55	0.85	0.55
Absorption													
Water solubility	-3.494	-4.21	-3.943	-4.443	-4.494	-4.116	-4.577	-2.907	-2.468	-4.362	-3.854	-4.9	-4.495
Caco2 permeability	1.07	1.126	0.401	1.401	1.419	0.572	0.841	1.347	-1.087	1.44	1.746	1.561	1.357
Intestinal absorption (human)	95.357	81.40	83.195	98.909	96.253	91.206	100	98.759	0	94.226	98.49	97.032	94.364
Skin Permeability	-3.794	-2.762	-3.156	-2.414	-2.591	-2.887	-3.159	-2.732	-2.735	-3.379	98.49	-2.725	-3.321
P-glycoprotein substrate	-	+	-	+	-	+	-	-	+	+	-	+	-
P-glycoprotein I inhibitor	-	-	-	-	-	+	+	-	-	+	-	-	+
P-glycoprotein II inhibitor	-	-	-	-	-	-	+	-	-	-	-	-	-
Distribution													
VDss (human)	-0.286	0.339	0.479	0.561	0.325	0.819	-0.288	-0.942	-0.62	-0.224	-0.827	-0.67	0.513
Fraction unbound (human)	0.281	0.379	0.405	0.142	0.059	0.044	0.079	0.184	0.477	0.208	0.047	0	0.099
BBB permeability	-0.598	-0.247	-0.362	0.447	0.302	-0.096	-0.915	-0.134	-2.029	0.348	0.065	0.074	0.095
CNS permeability	-2.691	-3.153	-3.028	-1.446	-1.494	-1.816	-3.036	-1.83	-5.56	-2.156	-1.746	-1.218	-1.949
Metabolism													
CYP2D6 substrate	-	-	-	-	-	-	-	-	-	-	-	-	-
CYP3A4 substrate	+	-	+	+	+	+	+	+	-	+	+	+	+
CYP1A2 inhibitor	-	+	-	+	+	-	-	-	-	-	-	-	-
CYP2C19 inhibitor	-	-	-	+	+	+	-	-	-	-	+	-	+
CYP2C9 inhibitor	-	-	-	-	+	-	-	-	-	-	-	+	-
CYP2D6 inhibitor	-	-	-	-	-	-	-	-	-	-	-	-	-
CYP3A4 inhibitor	-	-	-	-	-	-	-	-	-	-	-	-	-
Excretion													
Total clearance	1.183	0.271	0.484	0.209	0.821	0.28	0.497	0.507	0.691	1.037	1.23	1.07	0.511
Renal OCT2 substrate	-	-	-	-	-	-	-	-	-	-	-	-	-
Toxicity (Compound Number)													
AMES toxicity	-	-	-	-	-	-	-	-	-	-	-	-	-
Hepatotoxicity	-	+	-	+	-	-	-	-	-	-	+	-	-
hERG I inhibitors	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin Sensitization	+	-	-	-	-	-	-	-	-	-	-	-	-
Oral Rat Acute Toxicity (LD50)	2.162	2.166	3.107	2.453	2.649	2.192	3.32	1.954	1 2.597	1.669	1.789	2.738	2.435
Oral Rat Chronic Toxicity (LOAEL)	1	3.205	1.428	2.08	1.885	1.909	1.036	1.948	4.079	1.89	2.472	2.394	1.9

+ Sign signifies Yes, - Sign Signifies No

nuclear factor E2-related factor 2 (Nrf2) and the expression of superoxide dismutase (SOD) 1. Nrf2 is a key transcription factor involved in antioxidant responses, while SOD is an important enzyme that helps neutralize reactive oxygen species (ROS) in the body. At the same time, borneol downregulates the expression of NF-κB and p65, which are pro-inflammatory factors. By modulating the Nrf2/NF-κB pathway, borneol appears to inhibit the pro-inflammatory expression of cytokines, suggesting that it could potentially alleviate inflammation and oxidative damage in the pancreas. These studies offer valuable insights into the mechanisms by which these terpenes and terpenoids may exert their anti-inflammatory effects, highlighting their potential as candidates for the development of new anti-inflammatory drugs. However, further research is needed to fully understand their safety, efficacy, and potential clinical applications. Nonetheless, the findings represent exciting prospects for advancing our understanding of natural compounds in the treatment of inflammatory conditions and offer potential alternatives to traditional anti-inflammatory drugs (Kim et al., 2020).

2.8.3. *Immunomodulatory effects: harnessing the power of terpenoid*

Terpenoids are key elements found in biologically important fruits, vegetables, and spices that have a variety of pharmacological actions, particularly anticancer potential. Monoterpenoids, sesquiterpenoids, diterpenoids, sesterterpenoids, triterpenoids, tetraterpenoids, as well as polyterpenoids all block the NF-kB signalling pathway via IkB phosphorylation, DNA interaction, p65 translocation, and other mechanisms (Fig. 4) (Yang and Ping Dou, 2010). The transcription factor nuclear factor kappa B (NF-kB) is among the most significant inducible proteins in humans, known to govern gene expression in many crucial biological processes including such oxidative stress, inflammation, and etc, and has been linked to cancer development. The conventional (canonical) pathway and the option (non-canonical) pathway are the two signalling mechanisms that activate NF-B. The initiation of an enzyme IB kinase (IKK), which is found in intricate state consisting of catalytic kinase subunits (IKK/IKK) as well as the regulatory non-enzymatic protein NF-B essential modulator (NEMO), also known as IKK, is the universal regulatory phase in each of these pathways. Tumour necrosis factor (TNF) promotes and activates NF-B, which in turn stimulates the subunits of the IKK group and promotes to the phosphorylation and breakdown of IB inhibitors in the conventional or canonical route (Li and Verma, 2002). The conventional route activates RelA, c-Rel, RelB, and p50-containing NF-B dimers. This pathway is important in the regulation of host defense and inflammatory processes. The non-canonical route operates through the method of ligand-induced stimulation, which leads in the modulation of the pathway's core signalling element, NF-B-inducing kinase (NIK). NIK phosphorylates and triggers an IB kinase- (IKK) descending kinase, which then catalyses p100. Phosphorylation of p100 leads NF-B to be translocated to the nucleus, where it attaches to primary target genes for activation (Liu et al., 2017).

2.8.4. *Anti-allergic properties: addressing allergic disorders naturally*

Allergic diseases are characterized by inflammation, with specific immune cells like T cells and granulocytes (such as eosinophils, neutrophils, and mast cells) playing a crucial role. Among these cells, mast cells stand out as significant contributors to allergic conditions, particularly during the latter stages of the allergic response (Amin, 2012). Upon encountering an allergen, mast cells become activated and initiate the production of prostanoids and proinflammatory leukotrienes. Consequently, they release various inflammatory cytokines like IL-4, IL-5, IL-13, and IL-1α/β. These cytokines, in turn, trigger the activation of other immune cells, including neutrophils, monocytes, basophils, eosinophils, and lymphocytes, leading to a cascade of inflammatory

Table 4D
Absorption, distribution, metabolism, excretion, and toxicity (ADMET) characteristics (1) Petrosaspongiolides, (2) Petrosasponiolides-R, (3) Manoalide, (4) Spathulenol, (5) Cyclolinteinone, (6) Neomangicols-A, (7) Nitiol, (8) Variecolin, (9) Variecolol.

Sesterterpinoids	01	02	03	04	05	06	07	08	09
Drug-Likeness									
Lipinsk	+	+	+	+	+	+	+	+	+
Bioavailability score	0.55	0.55	0.55	0.55	0.55	0.56	0.56	0.55	0.55
Absorption									
Water solubility	-5.267	-3.191	-5.369	-3.818	-6.726	-4.674	-7.035	-6.244	-5.91
Caco2 permeability	1.125	0.783	0.811	1.4	1.242	0.678	1.235	1.336	1.309
Intestinal absorption (human)	100	100	92.571	94.833	95.516	74.262	94.28	100	96.057
Skin Permeability	-2.903	0.783	-3.454	-2.172	-2.93	-2.928	-2.713	-2.822	-3.133
P-glycoprotein substrate	-	-	+	-	-	+	-	-	-
P-glycoprotein I inhibitor	+	-	+	-	+	-	+	+	+
P-glycoprotein II inhibitor	+	+	+	-	+	+	-	+	+
Distribution									
VDss (human)	-0.142	-1.603	0.109	0.531	0.202	-0.327	0.655	0.324	0.405
Fraction unbound (human)	0	0	0.158	0.324	0	-0.895	0	0	0
BBB permeability	-0.444	0.161	0.141	0.605	-0.013	-0.895	0.654	0.052	0.617
CNS permeability	-1.799	-1.84	-2.134	-2.487	-2.168	-2.604	-2.105	-2.051	-2.249
Metabolism									
CYP2D6 substrate	-	-	-	-	-	-	-	-	-
CYP3A4 substrate	+	+	-	+	+	+	+	+	+
CYP1A2 inhibitor	-	-	-	-	-	-	-	-	-
CYP2C19 inhibitor	-	-	-	+	-	-	-	-	-
CYP2C9 inhibitor	-	-	-	-	-	-	-	-	-
CYP2D6 inhibitor	-	-	-	-	-	-	-	-	-
CYP3A4 inhibitor	-	-	-	-	-	-	-	-	-
Excretion									
Total clearance	0.072	0.37	0.887	0.895	1.021	-0.063	0.813	0.531	0.331
Renal OCT2 substrate	-	-	-	-	-	-	-	-	-
Toxicity (Compound Number)									
AMES toxicity	-	-	-	-	-	-	-	-	-
Hepatotoxicity	-	+	-	+	-	-	+	+	+
hERG I inhibitors	-	-	-	-	-	-	-	-	-
Skin Sensitization	-	-	-	-	-	-	-	-	-
Oral Rat Acute Toxicity (LD50)	2.6	2.675	2.789	1.737	1.904	2.177	1.652	1.79	1.998
Oral Rat Chronic Toxicity (LOAEL)	-0.311	1.29	1.885	1.422	2.215	2.204	0.969	1.915	2.004

+ Sign signifies Yes, - Sign Signifies No

reactions. Researchers have been actively exploring a wide range of anti-allergic compounds derived from diverse sources such as plants, animals, and microbes. These compounds exhibit varying mechanisms of action. Some directly bind to specific epitopes present in allergens, effectively interfering with the allergic response. Others exert their effects by influencing the gut microbiota and intestinal epithelial cells, thereby modulating immune responses. Additionally, certain compounds can modify antigen presentation and T cell differentiation, thereby regulating the immune system's sensitivity to allergens. Moreover, some anti-allergic compounds are known to inhibit the degranulation of effector cells, like mast cells, effectively reducing the release of inflammatory mediators (Amin, 2012).

The investigation of these anti-allergic compounds holds great promise for the development of innovative strategies to manage allergic diseases. By targeting different aspects of the allergic response, these compounds may offer novel and effective approaches to mitigate allergic reactions, providing much-needed relief for individuals suffering from allergic conditions. However, it is essential to conduct further research to gain a comprehensive understanding of the efficacy and safety of these compounds before they can be harnessed as viable therapeutic options for allergic diseases (Pratap et al., 2020).

2.8.5. Terpenoids and SARS-CoV-2: exploring potential antiviral effects

Terpenes, natural compounds derived from medicinal plants, have garnered attention as potential inhibitors of coronaviruses. They may function by blocking viral replication or targeting viral proteins essential for virus attachment and entry. The emergence of the severe and potentially fatal coronavirus disease (SARS-CoV-2) in late 2019 in Wuhan, China, prompted extensive global research on combatting this infectious disease. Among the investigations, the antiviral properties of various terpenoids have shown promise against SARS-CoV-2 infection (Das et al., 2021). Studies from around the world have explored prevention and treatment approaches, including vaccines and chemical compounds. RNA detection using a highly sensitive RT-PCR method has been successful in diagnosing SARS-CoV-2. Researchers have focused on testing terpenoids, flavonoids, phenols, glycosides, polyphenols, catechins, and other compounds for their inhibitory effects on glycoproteins like Mpro and Spike RBD, which are associated with ACE2 inhibition—the receptor used by the virus for entry. Terpenoids have demonstrated the ability to modulate viral protease activity, particularly through their interaction with 3CLpro also known as C30 endopeptidase or 3-chymotrypsin-like protease), a key protease found in coronaviruses (Udugama et al., 2020). Notably, essential oils such as lemon and geranium, along with their derivatives containing terpenoids like limonene and citronellol, have shown potential as natural antiviral agents against SARS-CoV-2. Ginkgolides, another class of terpenoids, exhibit antiviral effects by blocking the major protease of SARS-CoV-2. Triterpenoids, especially certain triterpenes, may hold promise in reversing the effects of CoV-2 Mpro, as suggested by pharmacokinetic profiles and docking scores. However, further in vitro and in vivo investigations are required to fully understand and evaluate their inhibitory potential. Andrographolide, a diterpenoid extracted from Andrographis paniculata, has been identified as a potential inhibitor of the primary SARS-CoV-2 protease (Mpro) using in silico methods (Saha et al., 2021). Molecular docking studies have also highlighted the binding affinity of compounds like thymol, carvacrol, hesperidine, and thymoquinone to the active site of Mpro. Tanshinones, derived from Salvia miltiorrhiza, have shown inhibitory effects on SARS-CoV-2 proteases 3CLpro and PLpro, with notable potency against PLpro. Betulinic acid, a triterpene extracted from Betula pubescens leaves, has exhibited high binding affinity to the receptor 6LU7, suggesting its potential as a therapeutic agent for SARS-CoV-2. Eucalyptol (1,8 cineole), found in

Table 4E
Absorption, distribution, metabolism, excretion, and toxicity (ADMET) characteristics (1) Ursolic acid, (2) Betulinic acid, (3) Lupeol, (4) Cealastrol, (5) Corticosterone, (6) Asiatic acid, (7) Madecassoside, (8) 3ß,6ß-Dihydroxyolean-12-en-27-oic acid (9) Spergulagenic acid.

Triterpenoids	01	02	03	04	05	06	07	08	09
Drug-Likeness									
Lipinsk	+	+	+	+	+	+	+	+	+
Bioavailability score	0.55	0.55	0.55	0.55	0.55	0.56	0.56	0.55	0.55
Absorption									
Water solubility	-3.635	-3.396	-5.922	-3.29	-3.466	-3.175	-2.794	-3.3	-2.846
Caco2 permeability	1.182	1.192	1.248	0.712	1.076	0.589	-0.886	0.596	0.466
Intestinal absorption (human)	97.377	100	97.882	100	96.614	68.215	0	100	66.376
Skin Permeability	-2.733	-2.735	-2.747	-2.735	-3.651	-2.735	-2.735	-2.735	-2.735
P-glycoprotein substrate	-	-	-	-	-	-	+	-	-
P-glycoprotein I inhibitor	-	-	+	-	+	-	+	-	-
P-glycoprotein II inhibitor	-	-	+	-	-	+	-	-	-
Distribution									
VDss (human)	-0.981	-1.118	0.023	-1.133	-0.268	-1.636	-0.513	-1.143	-1.301
Fraction unbound (human)	0.125	0.138	0.132	0.113	0.145	0.037	0.358	0.345	0.117
BBB permeability	-0.106	-0.375	0.747	0.081	0.042	-0.622	-2.258	-0.47	-0.596
CNS permeability	-1.211	-1.36	-1.781	-1.403	-2.154	-1.759	-5.093	-1.613	-1.683
Metabolism									
CYP2D6 substrate	-	-	-	-	-	-	-	-	-
CYP3A4 substrate	+	+	+	+	+	+	-	+	+
CYP1A2 inhibitor	-	-	-	-	-	-	-	-	-
CYP2C19 inhibitor	-	-	-	+	-	-	-	-	-
CYP2C9 inhibitor	-	-	-	-	-	-	-	-	-
CYP2D6 inhibitor	-	-	-	-	-	-	-	-	-
CYP3A4 inhibitor	-	-	-	-	-	-	-	-	-
Excretion									
Total clearance	0.083	0.116	0.153	-0.094	0.676	0.198	0.281	0	-0.077
Renal OCT2 substrate	-	-	-	-	-	-	-	-	-
Toxicity (Compound Number)									
AMES toxicity	-	-	-	-	-	-	-	-	-
Hepatotoxicity	+	+	-	+	-	+	-	+	+
hERG I inhibitors	-	-	-	-	-	-	-	-	-
Skin Sensitization	-	-	-	-	-	-	-	-	-
Oral Rat Acute Toxicity (LD50)	2.299	2.322	2.594	2.284	2.493	0.285	2.707	2.464	2.454
Oral Rat Chronic Toxicity (LOAEL)	2.06	2.249	0.917	2.068	1.409	1.499	4.451	2.059	1.986

+ Sign signifies Yes, - Sign Signifies No

eucalyptus essential oil, has also been identified through molecular docking as a potential inhibitor of SARS-CoV-2 infection (Astani and Schnitzler, 2014). Furthermore, linalool, a monoterpene mainly derived from lavender, has shown promising inhibitory effects on SARS-CoV-2 infection by binding with high affinity to the spike protein's receptor binding domain, potentially impeding virus-host ACE2 receptor binding and subsequent cellular internalization/release. These studies and findings highlight the potential of terpenoids in combating SARS-CoV-2 and provide avenues for further exploration in the development of therapeutics for SARS-CoV-2 The world of science was driven to look for novel antiviral formulations as a result of the SARS-CoV-2 virus pandemic brought on by this lethal virus and the scarcity of targeted medications. The most successful tactic in the current emergency circumstances may involve repurposing well-known traditional and/or licenced medications (Senthil Kumar et al., 2020). Terpenoids, which are generated from mevalonic acid, are made up of several isoprene structural units that are prevalent in environment. With higher than 50,000 chemicals identified from plants, these substances represent some of the most significant families of natural products (or secondary metabolites). In the relationship among plants as well as the ecosystem, many of them perform a vital and unusual ecological function, such as taking part in plant defence mechanisms (many of them are used as pesticides). It has been shown in previous years that several terpenoids have significant health-promoting benefits, including anticancer, anti-inflammatory, as well as antimicrobial, antiviral, and anti-plasmodium properties. Several of them have been demonstrated in experiments to block the coronavirus that causes severe acute respiratory syndrome. Phytochemicals, such as flavonoids, alkaloids, and terpene peptides, function as bioactive molecules and active components in plant species. Because these physiologically active chemicals are a component of the plant's defensive mechanism, they help to decrease infestations. These substances explorated, search, and thwart viral entrance and DNA/RNA replication as part of the therapeutic role. Among these, terpenes are the most prevalent and comprise a sizable class of secondary metabolites. They are made up of 5-C isoprene units that are intricately connected together. The majority of terpenoids are physiologically active and are utilised extensively across the world to treat a variety of diseases, such as artemisinin's antimalarial properties and Taxol derivatives used to treat cancer (Giofrè et al., 2021). Additionally, various in-silico studies have been carried out for the FDA-approved antiviral medications to distinguish novel phytochemical constituents anti-SARS-CoV-2. Some of the terpenoids like Limonene, Oleanolic acid, β-amyrin, Betulinic acid, β-sitosterol are predicted to block ACE2 and TMPRSS receptor and inhibit SARS-CoV-2 entry in the human body apart from this it's also activate CD4 and CD8 T-lymphocytes. Predicted mechanism of terpenoid that block viral protein required for replication (Fig. 5**).**

2.9. Pharmacological activity of terpenoids and essential oil

Terpenoids and essential oils play a fascinating role. Terpenoids, found in a variety of plants including herbs, spices, fruits, and trees, are known for their diverse properties. Essential oils, on the other hand, are concentrated extracts obtained from these plants, containing a rich mix of terpenoids and other bioactive compounds. The intriguing part is that both terpenoids and essential oils offer a wide range of pharmacological activities, making them not only valuable in traditional medicine but also essential in modern pharmaceutical research and the soothing realm of aromatherapy. pharmacological activities associated with terpenoids and essential oils (Fotsing Yannick Stephane and Kezetas Jean Jules, 2020), (Table 3).

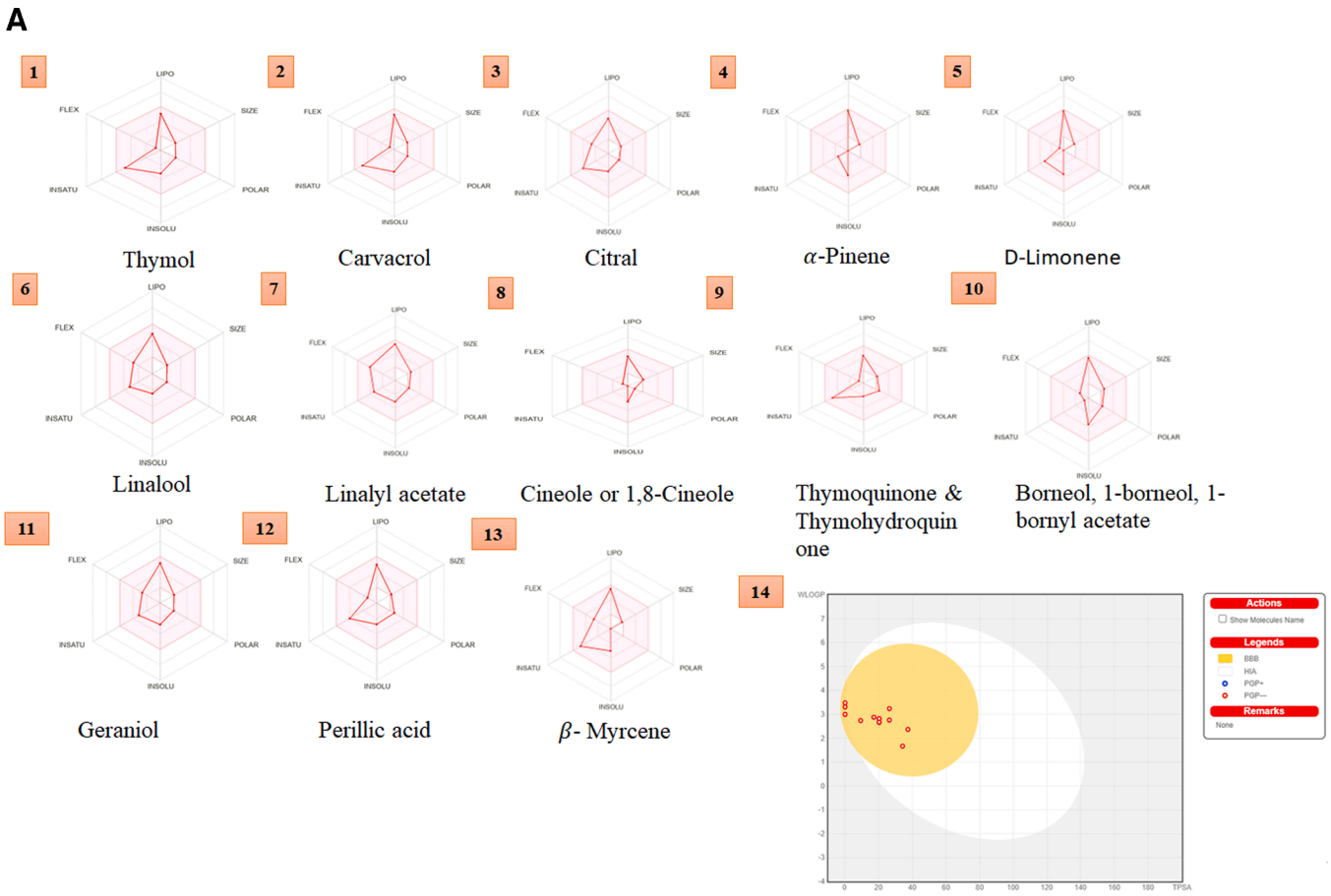

Fig. 6. A. Bioavailability radar of the selected monoterpenoids based on the physicochemical indices ideal for oral bioavailability. The pink area represents the optimal range for each property (lipophilicity: XLOGP3 between 1.67 to 4.57; size: MW between 136.23 to 196.29 g/mol; polarity: TPSA between 0 to 37.3 Å2; solubility: log S not higher than 9; saturation: fraction of carbons in the sp3 hybridization not greater than 1; and flexibility: no more than 6 rotatable bonds). (1) Thymol, (2) Carvacrol, (3) Citral, (4) α-Pinene, (5) D-Limonene, (6) Linalool, (7) Linalyl acetate, (8) Cineole or 1,8-Cineole, (9) Thymoquinone & Thymohydroquinone, (10) Borneol, 1-borneol, 1-bornyl acetate, (11) Geraniol, (12) Perillic acid, (13) β- Myrcene, (140) BOILED Egg simulation of monoterpenoids using the Swiss ADME simulator. BOILED Egg enables the intuitive assessment of passive gastrointestinal absorption (HIA) and brain penetration (BBB) based on the location of the metabolites in the WLOGP-against-TPSA referential. The white zone denotes a significant chance of passive absorption through the gastrointestinal system, whereas the yellow region (yolk) denotes a significant chance of brain penetration. The yolk and white portions do not have to be directly exclusive. Furthermore, the spots are coloured blue if they are projected to be effectively effluxed by P-gp (PGP+) and red if they are projected to be non-substrate of P-gp (PGP-). **B.** Bioavailability radar of the selected sesquiterpenoids based on the physicochemical indices ideal for oral bioavailability. The pink area represents the optimal range for each property (lipophilicity: XLOGP3 between 0.9 to 5.42; size: MW between 216.32 and 306.52 g/mol; polarity: TPSA between 17.07 and 72.83 Å2; solubility: log S not higher than 4; saturation: fraction of carbons in the sp3 hybridization not higher than 0.73; and flexibility: no more than 7 rotatable bonds) (1) Turmerone, (2) Curcumolide, (3) Farnesol, (4) Nerolidol, (5) Zerumbone, (6) Valerenic acid, (7) Ziniolide, (8) α-Bisabolol (9) Matricine, (10) Curdione (11) Germacrone, (12) BOILED Egg simulation of sesquiterpenoids using the Swiss ADME simulator. BOILED Egg enables the intuitive assessment of passive gastrointestinal absorption (HIA) and brain penetration (BBB) based on the location of the metabolites in the WLOGP-against-TPSA referential. The white zone denotes a significant chance of passive absorption through the gastrointestinal system, whereas the yellow region (yolk) denotes a significant chance of brain penetration. The yolk and white portions do not have to be directly exclusive. Furthermore, the spots are coloured blue if they are projected to be effectively effluxed by P-gp (PGP+) and red if they are projected to be non-substrate of P-gp (PGP-). **C.** Bioavailability radar of the the diterpenoids based on the physicochemical indices ideal for oral bioavailability. The pink area represents the optimal range for each property (lipophilicity: XLOGP3 between −0.7 and +5.0; size: MW between 150 and 500 g/mol; polarity: TPSA between 20 and 130 Å2; solubility: log S not higher than 6; saturation: fraction of carbons in the sp3 hybridization not less than 0.25; and flexibility: no more than 9 rotatable bonds) (1) Andrographolide, (2) Ginkgolides, (3) Triptolide, (4) Tanshinone, (5) Tanshinone IIA, (6) Carnosol, (7) Salvinorin A, (8) Steviol, (9) Stevioside, (10) Austroinulin, (11) Communic acid, (12) Copallic acid, (13) Kahweol, (14) BOILED Egg simulation of diterpenoids using the Swiss ADME simulator. BOILED Egg enables the intuitive assessment of passive gastrointestinal absorption (HIA) and brain penetration (BBB) based on the location of the metabolites in the WLOGP-against-TPSA referential. The white zone denotes a significant chance of passive absorption through the gastrointestinal system, whereas the yellow region (yolk) denotes a significant chance of brain penetration. The yolk and white portions do not have to be directly exclusive. Furthermore, the spots are coloured blue if they are projected to be effectively effluxed by P-gp (PGP+) and red if they are projected to be non-substrate of P-gp (PGP-). **D.** Bioavailability radar of the sesterterpenoids based on the physicochemical indices ideal for oral bioavailability. The pink area represents the optimal range for each property (lipophilicity: XLOGP3 between 1.26 to 6.4; size: MW between 220.35 to 460.6 g/mol; polarity: TPSA between 20.23 and 101.15 Å2; solubility: log S not higher than 7; saturation: fraction of carbons in the sp3 hybridization not less than 0.93; and flexibility: no more than 9 rotatable bonds) (1) Petrosaspongiolides, (2) Petrosasponiolides-R, (3) Manoalide, (4) Spathulenol, (5) Cyclolinteinone, (6) Neomangicols-A, (7) Nitiol, (8) Variecolin, (9) Variecolol, (10) BOILED Egg simulation of sesterterpenoids using the Swiss ADME simulator. BOILED Egg enables the intuitive assessment of passive gastrointestinal absorption (HIA) and brain penetration (BBB) based on the location of the metabolites in the WLOGP-against-TPSA referential. The white zone denotes a significant chance of passive absorption through the gastrointestinal system, whereas the yellow region (yolk) denotes a significant chance of brain penetration. The yolk and white portions do not have to be directly exclusive. Furthermore, the spots are coloured blue if they are projected to be effectively effluxed by P-gp (PGP+) and red if they are projected to be non-substrate of P-gp (PGP-). **E.** Bioavailability radar of the triterpenoids based on the physicochemical indices ideal for oral bioavailability. The pink area represents the optimal range for each

property (lipophilicity: XLOGP3 between −1.24 and 9.87; size: MW between 346.46 and 975.12 g/mol; polarity: TPSA between 20.23 and 335.44 Å2; solubility: log S not higher than 7; saturation: fraction of carbons in the sp3 hybridization not less than 0.94; and flexibility: no more than 10 rotatable bonds) (1) Ursolic acid, (2) Betulinic acid, (3) Lupeol, (4) Cealastrol, (5) Corticosterone, (6) Asiatic acid, (7) Madecassoside, (8) 3ß,6ß-Dihydroxyolean-12-en-27-oic acid (9) Spergulagenic acid, (10) BOILED Egg simulation of triterpenoids using the Swiss ADME simulator. BOILED Egg enables the intuitive assessment of passive gastrointestinal absorption (HIA) and brain penetration (BBB) based on the location of the metabolites in the WLOGP-against-TPSA referential. The white zone denotes a significant chance of passive absorption through the gastrointestinal system, whereas the yellow region (yolk) denotes a significant chance of brain penetration. The yolk and white portions do not have to be directly exclusive. Furthermore, the spots are coloured blue if they are projected to be effectively effluxed by P-gp (PGP+) and red if they are projected to be non-substrate of P-gp (PGP-).

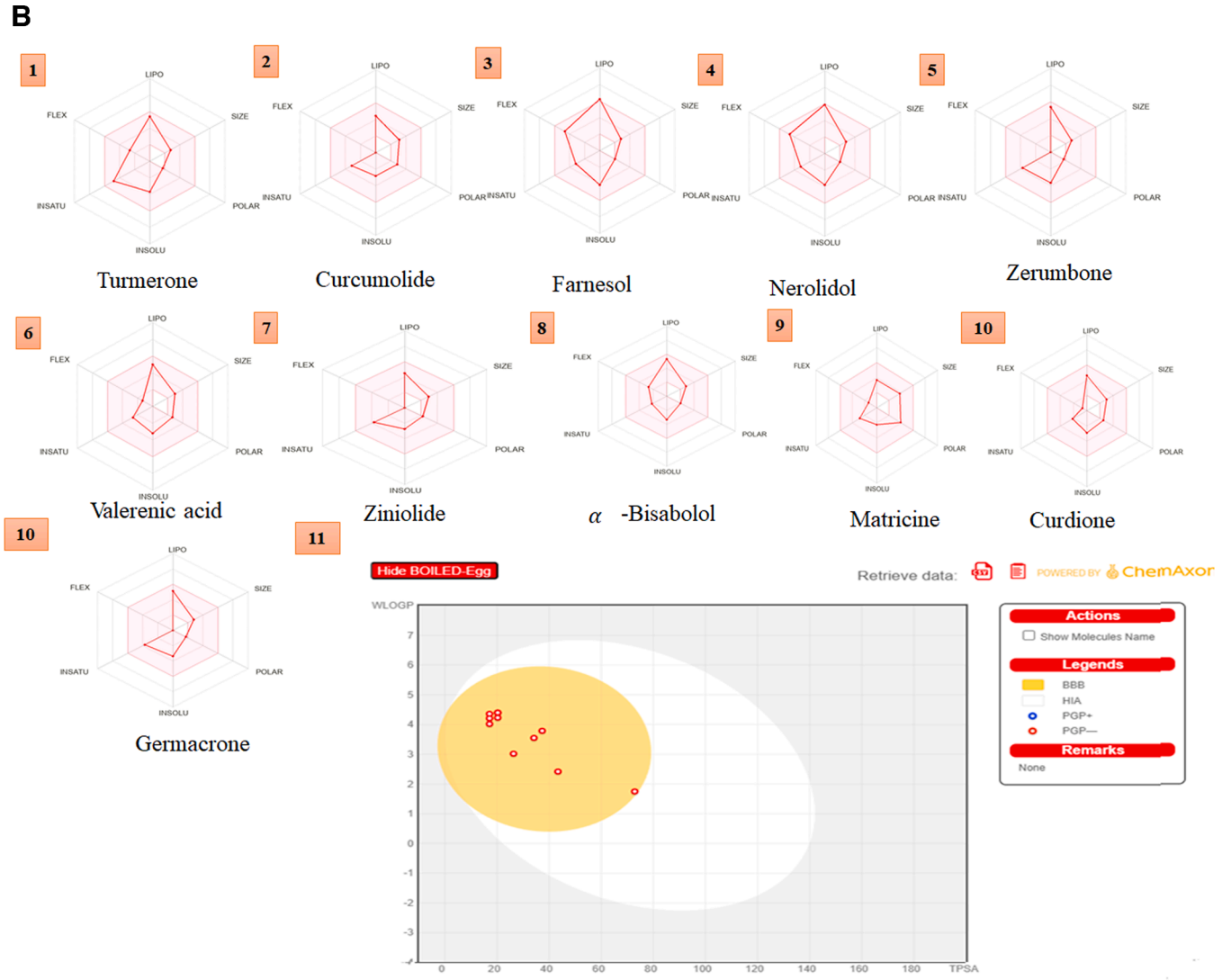

Fig. 6. (*continued*).

2.9.1. Antioxidant

The power of terpenoids and essential oils extends to their antioxidant prowess. With the ability to neutralize harmful free radicals and combat oxidative stress, they stand as defenders against chronic diseases and aging-related concerns (Gutiérrez-Del-río et al., 2021).

2.9.2. Antimicrobial

The realm of terpenoids and essential oils includes a vast array of natural antimicrobials. These compounds stand as defenders against microbes, thwarting the growth of bacteria, fungi, and even some viruses. As a result, they're gaining attention as natural alternatives to traditional antibiotics (Chouhan et al., 2017).

2.9.3. Anticancer

In the realm of potential cancer research, specific terpenoids and essential oils have shown promise. Their unique properties demonstrate cytotoxic effects on cancer cells, affecting their growth cycle, inducing programmed cell death, and potentially inhibiting tumor expansion (Blowman et al., 2018)

2.9.4. Analgesic and anti-nociceptive

The relief offered by terpenoids and essential oils extends to pain management. By interacting with pain receptors and neurotransmitters, they provide a natural means of alleviating discomfort and pain, whether applied topically or inhaled aromatically (Sarmento-Neto et al., 2016).

2.9.5. Anxiolytic and sedative

The realm of terpenoids and essential oils isn't just about physical benefits; it extends to the mind as well. Certain compounds have a calming effect on the nervous system, offering solace to those dealing with anxiety and stress. Aromatherapy becomes a sanctuary of

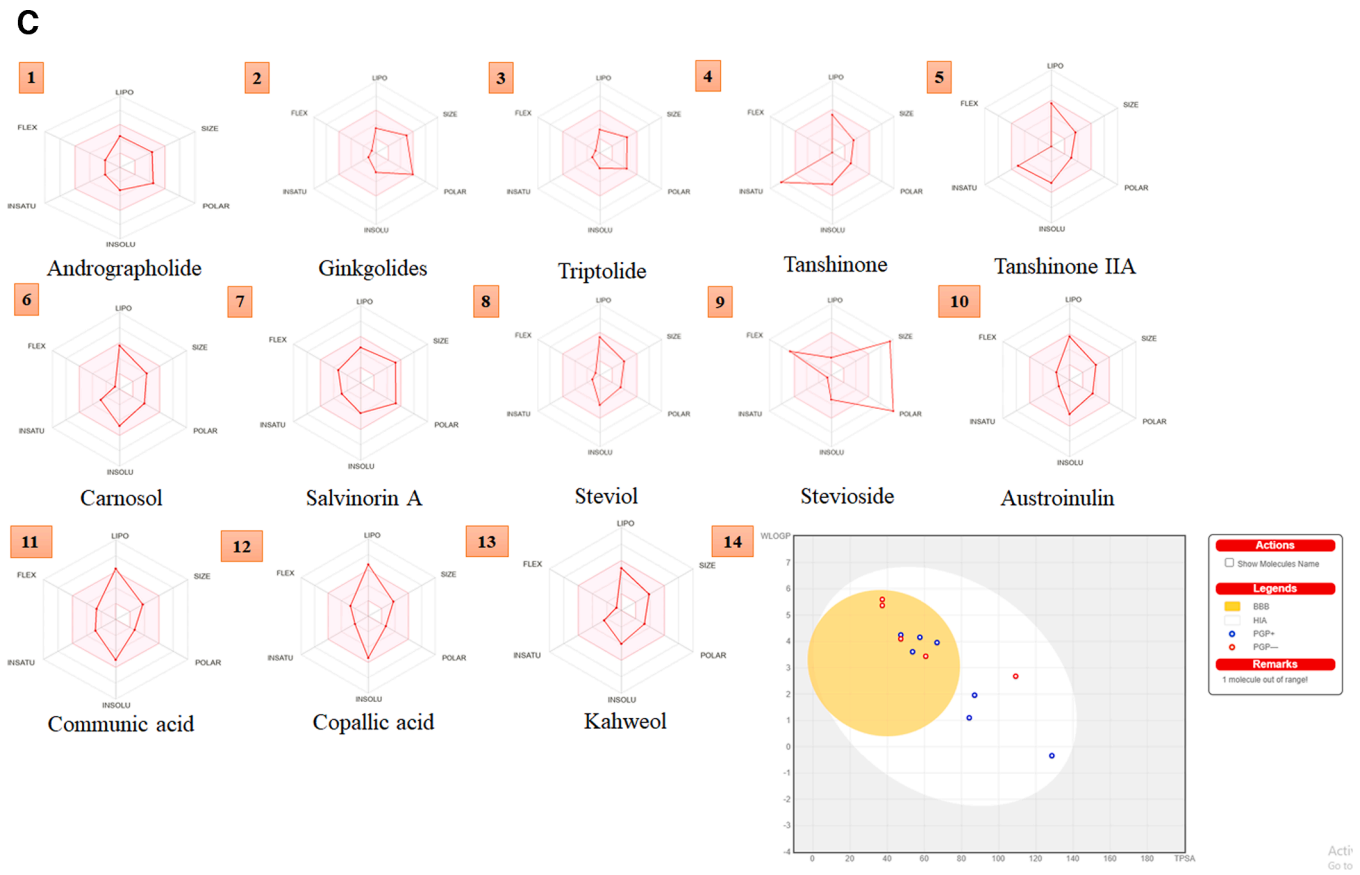

Fig. 6. (*continued*).

relaxation and tranquility (Agatonovic-Kustrin et al., 2020).

2.9.6. *Immunomodulatory*

The immune system finds a friend in terpenoids and essential oils. By enhancing immune cell function or taming immune hyperactivity, they promote a balanced and harmonious immune response that supports overall well-being (Sandner et al., 2020).

2.9.7. *Cardiovascular effects*

Some terpenoids step up to the task of supporting cardiovascular health. They contribute by assisting in the regulation of cholesterol levels and blood pressure, offering a potential defense against heart-related concerns (Shaito et al., 2020).

2.9.8. *Gastrointestinal effects*

The gastrointestinal realm finds solace in terpenoids and essential oils. Their properties extend to alleviating symptoms of conditions like gastritis and irritable bowel syndrome, providing relief where it's needed (Chumpitazi et al., 2018) .

2.9.9. *Respiratory effects*

When it comes to respiratory health, essential oils containing terpenoids come to the rescue. Inhaled through aromatherapy or other means, these oils ease congestion, coughs, and even respiratory infections (Horváth and Ács, 2015)

2.10. *Terpenoids' mineral and trace element content: implications for health*

Micronutrients, including zinc, selenium, and copper, are essential for various reasons, particularly due to their antiviral and anti-inflammatory properties. Zinc, as a trace element, plays a crucial role in boosting the immune system, supporting growth, and aiding in wound healing. Deficiency in zinc has been associated with severe immune dysfunctions. Supplementing with zinc has shown promising results in restoring taste in these patients. Zinc is also known to inhibit several RNA viruses, including SARS-CoV. Zinc deficiency can significantly impair immune function, incsing the risk of infections such as pneumonia. Zinc supplementation has been found to protect against respiratory tract infions like the common cold. Zinc deficiency affects approximately 2 billion people worldwide, with older adults being particularly susceptible. Including dietary sources of zinc, such as meat, shellfish, legumes, nuts, and whole grains, is recommended to obtain its benefits. Selenium, another essential mineral, has been identified as a protective factor against certain viruses, including HIV. Selenium-rich foods like whole grains, dairy products, and seafood contribute to immune health. Consuming functional foods rich in zinc and selenium may help reduce the risks associated with common cold. Copper, an essential mineral for both the host and pathogen during viral infections, plays a role in the bioactivities of important blood cells involved in killing infectious microbes and producing antibodies. Copper deficiency can lead to increased vulnerability to infections due to reduced quantity and impaired activities of blood cells. Furthermore, copper has the ability to destroy several viruses (Ferreira et al., 2021). Medical plants that contain terpenoids are known to have varying mineral and trace element content. Here are some examples:

2.10.1. *Ginseng (Panax ginseng)*

Ginseng is a popular medicinal plant known for its adaptogenic properties. It contains minerals such as potassium, calcium, magnesium, and phosphorus, along with trace elements like iron, zinc, copper, and manganese (Wee et al., 2011).

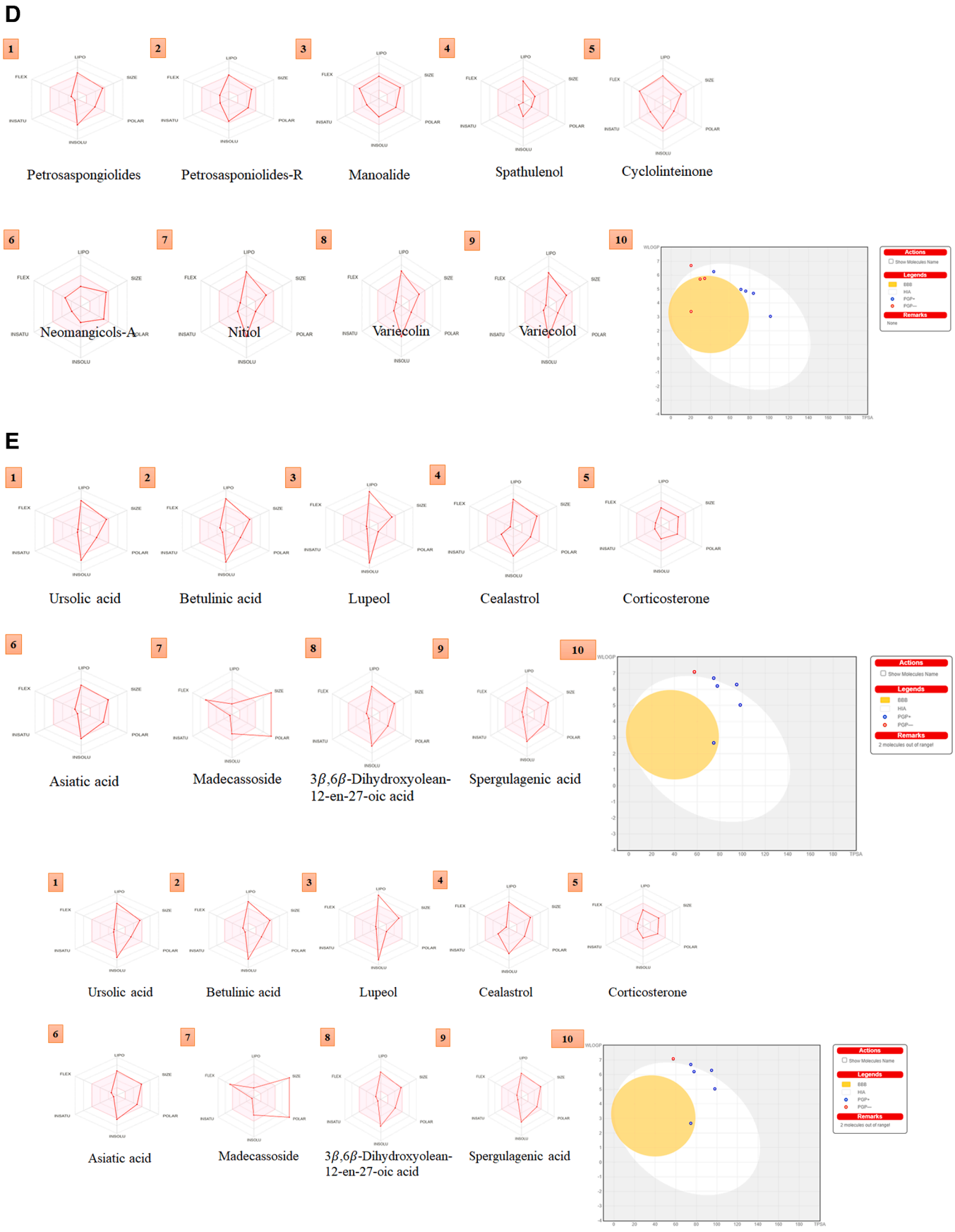

Fig. 6. (*continued*).

2.10.2. Turmeric (Curcuma longa)

Turmeric is a spice commonly used in traditional medicine. It contains minerals such as potassium, calcium, and magnesium, as well as trace elements like iron and manganese (Kumaravel and Alagusundaram, 2014).

2.10.3. Ginkgo biloba

Ginkgo biloba is a tree species known for its medicinal properties. It contains minerals such as calcium, magnesium, and phosphorus, and trace elements like zinc and copper (Noor-E-Tabassum et al., 2022).

2.10.4. Garlic (Allium sativum)

Garlic is a well-known medicinal plant with various health benefits. It contains minerals such as potassium, calcium, and magnesium, and trace elements like selenium and manganese (Lidiková et al., 2023).

2.10.5. Peppermint (Mentha piperita)

Peppermint is a widely used medicinal herb. It contains minerals such as calcium, magnesium, and potassium, along with trace elements like iron and manganese (Herro and Jacob, 2010).

2.10.6. Echinacea (Echinacea purpurea)

Echinacea is a popular herb used for its immune-boosting properties. It contains minerals such as calcium, magnesium, and phosphorus, and trace elements like zinc and copper (Manayi et al., 2015).

2.11. Pharmacokinetic and toxicity (ADMET) properties of selected terpenoids

The limited properties of absorption, distribution, metabolism, excretion, and toxicity (ADMET) can potentially diminish the effectiveness of a promising drug. Pharmacokinetic characteristics, which can be costly to study in clinical trials, are considered a major drawback in drug discovery. To assess the potential of selected terpenoids as candidates for pharmaceutical synthesis, in silico methods were employed to calculate their ADMET factors (Refer to Tables 4 A, B, C, D, E). It is interesting to note that the majority of the selected terpenoids comply with Lipinski's rule of five, and some also meet the Ghose, Veber, and Egan criteria, indicating a high potential for bioavailability. The solubility of the compounds in water, as indicated by aqueous solubility values, is another important characteristic for their absorption and distribution in the body. The results reveal that most of the compounds exhibit good water solubility. Assessing the permeability of the skin, which determines the rate at which a molecule penetrates the stratum corneum, is crucial for identifying the potential of transdermal drug administration. A molecule is considered to penetrate the epidermis when its log Kp value exceeds 2.5 cm/h. All of the selected terpenoids were found to have moderate to good skin absorption. The Caco-2 permeability assay, using human epithelial colorectal adenocarcinoma cells, can estimate the extent of oral drug absorption. Most of the terpenoids demonstrated moderate to strong Caco-2 permeability scores (log Papp values > 0.90 cm/s). ADMET assessment, a software-based drug development method, can aid in the early stages of drug development (Kamran et al., 2022). The in silico technique offers a more time and cost-efficient approach compared to traditional ADMET profiling. While the wet lab (in vitro cell culture) method would take over ten weeks to analyze around 20,000 drugs, the computational in silico method can perform the analysis almost instantaneously. As a result, the pharmaceutical industry has increasingly adopted this computational strategy for pharmaceutical analysis since the introduction of the ADMET dataset in the 1990s. In this study, we utilized the Swiss ADME and pkCSM programs to predict the pharmacokinetic characteristics and low toxicity of the identified bioactive constituents. The computational analysis provides valuable insights that can enhance the development of potential semi-synthetic and synthetic medications for various applications. Most of the selected terpenoids were found not to be P-gp substrates or inhibitors. P-gp, or ATP-binding cassette transporters, is a key component of the ABC transporter family responsible for protecting the central nervous system (CNS) against toxic compounds and mediating active efflux across bio membranes. In terms of digestibility, it was observed that the majority of terpenoids were well absorbed by the gut. The assessment of epidermis permeability using Log KP revealed that the selected terpenoids demonstrated a high-to-moderate level of penetration into the skin, indicating their drug-like properties. Regarding the blood-brain barrier (BBB), certain monoterpenoids, sesquiterpenoids, sesterterpenoids, and triterpenoids showed a higher probability of BBB penetration based on their log BB values. However, only a few molecules from each terpenoid subclass were found to enter the brain. In terms of tissue distribution, several terpenoids exhibited effective dispersion volumes (logVDss) in organs, indicating their potential for distribution throughout the body. Evaluation of human cytochrome P450 (CYP) subtypes involved in hepatic drug metabolism revealed that most of the terpenoids were not inhibitors or substrates of CYP3A4, the primary drug-metabolizing enzyme in humans. Inhibition of CYP3A4 can lead to systemic toxicity and drug interactions. The majority of the terpenoids also demonstrated good total clearance, indicating their potential for efficient elimination through liver and kidney pathways. Toxicity assessment of the selected terpenoids was performed using various criteria such as AMES toxicity, liver toxicity, hERG sodium-potassium suppression, and skin sensitization. The findings indicated that only a small number of terpenoids showed potential mutagenesis and liver toxicity effects, suggesting that the majority of terpenoids pose no significant toxic concerns. Additionally, the bioavailability radar data showed that the discovered phytochemicals exhibited enhanced bioavailability and drug-like properties based on parameters such as lipophilicity, polarity, size, saturation, solubility, and flexibility. The evaluation of central nervous system and intestinal permeability using the BOILED Egg model provided insights into gastrointestinal uptake and BBB permeation for each compound. Compounds denoted by a red spot in the yellow circular region were identified as non-substrates of P-gp, indicating their potential to penetrate the brain. These findings contribute to the understanding of the pharmacological potential of the identified terpenoids, particularly their pro inflammatory activities. Overall, the computational analysis employed in this study offers valuable insights into the pharmacokinetic characteristics, toxicity, and drug-like properties of the selected terpenoids, facilitating the development of potential pharmaceutical applications (Fig. 6 A-E).

3. Concluding remarks: unlocking the potential of terpenoids and essential oils

The exploration of natural products in drug development has been hindered by the laborious extraction and isolation processes. However, advancements in technology have spurred the creation of rapid, automated techniques, promising high-throughput screening capabilities for extracting and separating these compounds. Modern extraction methods, including steam distillation, solvent extraction, UAE, MAE, SFE, and PLE, have gained attention due to their superior extraction yields and safety merits, becoming routine analytical preparation methods. Furthermore, research into novel packing materials and hybrid techniques like LC-NMR and LC-MS offer potential solutions to streamline the isolation process, despite the persisting challenge of isolating pure compounds from complex mixtures. The growing interest in natural product extraction and its applications has steered the development of extraction methods and innovative phases for more efficient techniques. This trend, driven by consumer demands and considerations of safety, environment, and regulations, is expected to persist. In conclusion, the evolution of extraction and isolation methodologies signifies a burgeoning interest in maximizing the potential of natural products. The ongoing advancements underscore the need for continued research to overcome extraction complexities and harness the full benefits of these

compounds. Prioritizing these advancements aligns with the evolving landscape of consumer needs and broader societal considerations, emphasizing the importance of sustainable and efficient utilization of natural resources in drug development.

4. Future perspectives: expanding applications in medicine and beyond

Future research efforts should focus on elucidating the specific mechanisms of action of terpenes and terpenoids in different medical conditions. This knowledge can guide the development of targeted therapies and pharmaceutical formulations that harness the full potential of these bioactive compounds. Additionally, exploring the synergistic effects of combining various terpenes and terpenoids may lead to the discovery of novel therapeutic combinations with enhanced efficacy and reduced side effects. This could revolutionize the field of natural medicine and pave the way for new treatment options. Furthermore, advancements in extraction techniques and processing technologies are essential to improve the yield and quality of EOs, making them more accessible and cost-effective for pharmaceutical applications. As we move forward, it is imperative to prioritize safety assessments and environmental impact studies to ensure responsible use and application of essential oils. Collaboration between researchers, industry experts, and regulatory bodies is essential to establish guidelines and standards for the incorporation of EOs into various products while maintaining consumer safety and environmental sustainability.

Funding

This research received no external funding.

Author agreement statement

We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We understand that the Corresponding Author is the sole contact for the Editorial process. He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs

CRediT authorship contribution statement

Tohfa Siddiqui: Conceptualization, Writing – review & editing, Methodology, Data curation, Writing – original draft. **Mohammad Umar Khan:** Investigation. **Vikram Sharma:** Visualization. **Komal Gupta:** Data curation, Writing – review & editing, Methodology.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgements

The author gratefully acknowledges the Galgotias college of pharmacy, Knowledge park-II, greater Noida-201306, India

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